Chapter 2

Transporters, receptors, and enzymes as targets of psychopharmacological drug action

Psychotropic drugs have many mechanisms of action, but they all target specific molecular sites that have profound effects upon neurotransmission. It is thus necessary to understand the anatomical infrastructure and chemical substrates of neurotransmission (Chapter 1) in order to grasp how psychotropic drugs work. Although there are over 100 essential psychotropic drugs utilized in clinical practice today (see *Stahl's Essential Psychopharmacology: the Prescriber's Guide*), there are only a few sites of action for all these therapeutic agents (Figure 2-1). Specifically, about a third of psychotropic drugs target one of the transporters for a neurotransmitter; another third target receptors coupled to G proteins; and perhaps only 10% target enzymes. All three of these sites of action will be discussed in this chapter. The balance of psychotropic drugs target various types of ion channels, which will be discussed in Chapter 3. Thus, mastering how just a few molecular sites regulate neurotransmission allows the psychopharmacologist to understand the theories about the mechanisms of action of virtually all psychopharmacological agents.

Neurotransmitter transporters as targets of drug action

Classification and structure

Neuronal membranes normally serve to keep the internal milieu of the neuron constant by acting as barriers to the intrusion of outside molecules and to the leakage of internal molecules. However, selective permeability of the membrane is required to allow discharge as well as uptake of specific molecules, to respond to the needs of cellular functioning. Good examples of this are neurotransmitters, which are released from neurons during neurotransmission and, in many cases, are also transported back into presynaptic neurons as a recapture mechanism following their release. This recapture – or reuptake – is done in order for neurotransmitter to be reused in a subsequent neurotransmission. Also, once inside the neuron, most neurotransmitters are transported again into synaptic vesicles for storage, protection from metabolism, and immediate use during a volley of future neurotransmission.

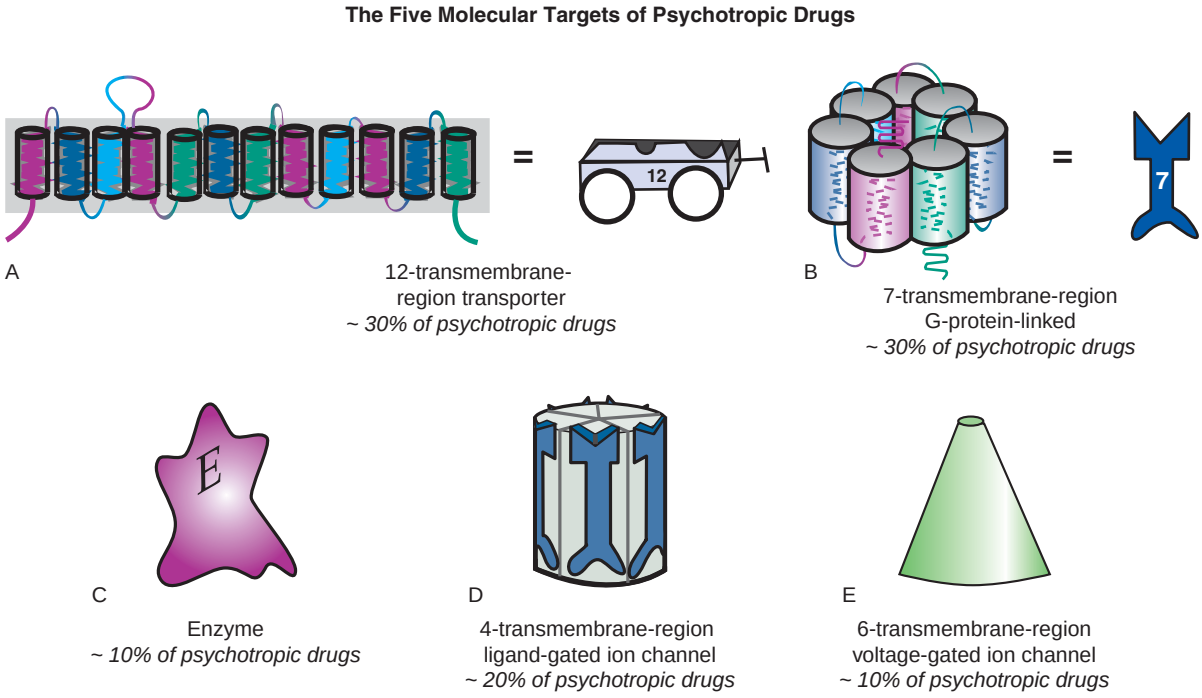


Figure 2-1. The molecular targets of psychotropic drugs. There are only a few major sites of action for the wide expanse of psychotropic drugs utilized in clinical practice. Approximately one-third of psychotropic drugs target one of the twelve-transmembrane-region transporters for a neurotransmitter (A), while another third target seven-transmembrane-region receptors coupled to G proteins (B). The sites of action for the remaining third of psychotropic drugs include enzymes (C), four-transmembrane-region ligand-gated ion channels (D), and six-transmembrane-region voltage-sensitive ion channels (E).

Both types of neurotransmitter transport – presynaptic reuptake as well as vesicular storage – utilize a molecular transporter belonging to a "superfamily" of twelve-transmembrane-region proteins (Figures 2-1A and 2-2). That is, neurotransmitter transporters have in common the structure of going in and out of the membrane 12 times (Figure 2-1A). These transporters are a type of receptor that binds to the neurotransmitter prior to transporting that neurotransmitter across the membrane.

Recently, details of the structures of neurotransmitter transporters have been determined; this has led to a proposed subclassification of neurotransmitter transporters. That is, there are two major subclasses of *plasma membrane transporters* for neurotransmitters. Some of these transporters are presynaptic and others are on glial membranes. The first subclass consists of sodium/chloride-coupled transporters, called the solute carrier SLC6 gene family, and includes transporters for the monoamines serotonin, norepinephrine, and dopamine (Table 2-1 and Figure 2-2A) as well as for the neurotransmitter GABA (gamma-aminobutyric acid) and the amino acid glycine (Table 2-2 and Figure 2-2A). The second subclass consists of high-affinity glutamate transporters, also called the solute carrier SLC1 gene family (Table 2-2 and Figure 2-2A).

In addition, there are three subclasses of *intracellular synaptic vesicle transporters* for neurotransmitters. The SLC18 gene family comprises the vesicular monoamine transporters (VMATs) for serotonin, norepinephrine, dopamine, and histamine and the vesicular acetylcholine transporter (VAChT). The SLC32 gene family consists of the vesicular inhibitory amino acid transporters (VIAATs). Finally, the SLC17 gene family consists of the vesicular glutamate transporters, such as VGluT1–3 (Table 2-3 and Figure 2-2B).

Monoamine transporters (SLC6 gene family) as targets of psychotropic drugs

Reuptake mechanisms for monoamines utilize unique presynaptic transporters (Figure 2-2A) but the same vesicular transporter in all three monoamine neurons (histamine neurons also use the same vesicular

Table 2-1 Presynaptic monoamine transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate	False substrate
Serotonin transporter	SERT	SLC6	Serotonin	Ecstasy (MDMA)
Norepinephrine transporter	NET	SLC6	Norepinephrine	Dopamine Epinephrine Amphetamine
Dopamine transporter	DAT	SLC6	Dopamine	Norepinephrine Epinephrine Amphetamine

MDMA, 3,4-methylenedioxymethamphetamine

Table 2-2 Neuronal and glial GABA and amino acid transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate
GABA transporter 1 (neuronal and glial)	GAT1	SLC6	GABA
GABA transporter 2 (neuronal and glial)	GAT2	SLC6	GABA β-alanine
GABA transporter 3 (mostly glial)	GAT3	SLC6	GABA β-alanine
GABA transporter 4, also called betaine transporter (neuronal and glial)	GAT4 BGT1	SLC6	GABA betaine
Glycine transporter 1 (mostly glial)	GlyT1	SLC6	Glycine
Glycine transporter 2 (neuronal)	GlyT2	SLC6	Glycine
Excitatory amino acid transporters 1–5	EAAT1–5	SLC1	L-glutamate L-aspartate

transporter) (Figure 2-2B). That is, the unique presynaptic transporter for serotonin is known as SERT, for norepinephrine is known as NET, and for dopamine is known as DAT (Table 2-1 and Figure 2-2A). All three of these monoamines are then transported into synaptic vesicles of their respective neurons by the same vesicular transporter, known as VMAT2 (vesicular monoamine transporter 2) (Figure 2-2B and Table 2-3).

Although the three presynaptic transporters – SERT, NET, and DAT – are unique in their amino acid sequences and binding affinities for monoamines, each presynaptic monoamine transporter nevertheless has appreciable affinity for amines other than the one matched to its own neuron (Table 2-1). Thus, if other transportable neurotransmitters or drugs are in the vicinity of a given monoamine transporter, they may also be transported into the presynaptic neuron by hitchhiking a ride on certain transporters that can carry them into the neuron.

For example, the norepinephrine transporter (NET) has high affinity for the transport of dopamine as well as for norepinephrine, the dopamine transporter (DAT) has high affinity for the transport of amphetamines as well as for dopamine, and the serotonin transporter (SERT) has high affinity for the transport of "ecstasy" (the drug of abuse MDMA or 3,4-methylenedioxymethamphetamine) as well as for serotonin (Table 2-1).

How are neurotransmitters transported? Monoamines are not passively shuttled into the presynaptic neuron, because it requires energy to concentrate monoamines into a presynaptic neuron. That energy is provided by transporters in the SLC6 gene family coupling the "downhill" transport of sodium (down a concentration gradient) with the "uphill" transport of the monoamine (up a concentration gradient) (Figure 2-2A). Thus, the monoamine transporters are really sodium-dependent cotransporters; in most cases, this involves the additional cotransport of chloride, and in some cases the countertransport of

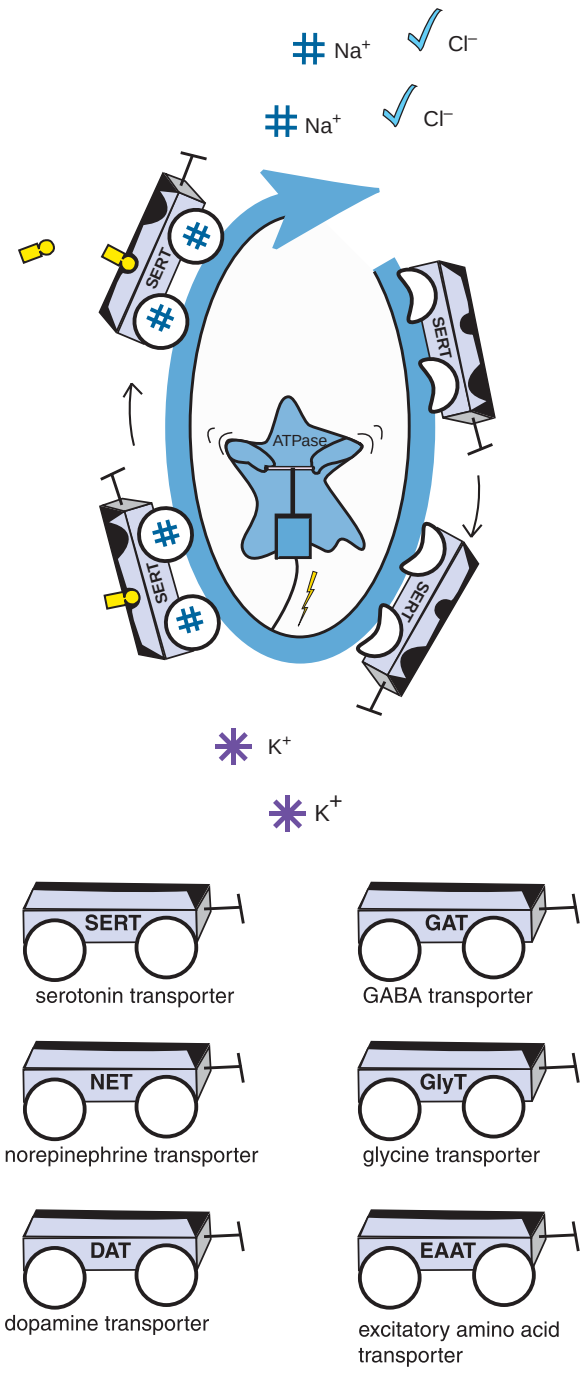


Figure 2-2A. Sodium-potassium ATPase. Transport of many neurotransmitters into the presynaptic neuron is not passive, but rather requires energy. This energy is supplied by sodium-potassium ATPase (adenosine triphosphatase), an enzyme that is also sometimes referred to as the sodium pump. Sodium-potassium ATPase continuously pumps sodium out of the neuron, creating a downhill gradient. The "downhill" transport of sodium is coupled to the "uphill" transport of the neurotransmitter. In many cases this also involves cotransport of chloride and in some cases countertransport of potassium. Examples of neurotransmitter transporters include the serotonin transporter (SERT), the norepinephrine transporter (NET), the dopamine transporter (DAT), the GABA transporter (GAT), the glycine transporter (GlyT), and the excitatory amino acid transporter (EAAT).

potassium. All of this is made possible by coupling monoamine transport to the activity of sodium-potassium ATPase (adenosine triphosphatase), an enzyme sometimes called the "sodium pump" that creates the downhill gradient for sodium by continuously pumping sodium out of the neuron (Figure 2-2A).

The structure of a monoamine transporter from the SLC6 family has recently been proposed to have binding sites not only for the monoamine, but also for two sodium ions (Figure 2-2A). In addition, these transporters may exist as dimers, or two copies working together with each other, but the manner in which they cooperate is not yet well understood and is not shown in the figures. There are other sites on this transporter – not well defined – for drugs such as antidepressants, which bind to the transporter and inhibit reuptake of monoamines but do not bind to the substrate site and are not transported into the neuron (thus they are *allosteric*, meaning "other site").

In the absence of sodium, there is low affinity of the monoamine transporter for its monoamine substrate, and thus binding of neither sodium nor monoamine. An example of this is shown for the serotonin transporter SERT in Figure 2-2A, where some of the transport "wagons" have flat tires, indicating no binding of sodium as well as absence of binding of serotonin to its substrate binding site, since the transporter has low affinity for serotonin in the absence of sodium. The allosteric site for antidepressant binding is also empty (the front seat in Figure 2-2A). However, in the presence of sodium ions, the tires are "inflated" by sodium binding and serotonin can also bind to its substrate site on SERT. The situation is now primed for serotonin transport back into the serotonergic neuron, along with cotransport of sodium and chloride down the gradient and into the neuron and countertransport of potassium out of the neuron (Figure 2-2A). But if a drug binds to an inhibitory allosteric site on SERT, this reduces the affinity of the serotonin transporter SERT for its substrate serotonin, and serotonin binding is prevented.

Table 2-3 Vesicular neurotransmitter transporters

Transporter	Common abbreviation	Gene family	Endogenous substrate
Vesicular monoamine transporters 1 and 2	VMAT1 VMAT2	SLC18	Serotonin Norepinephrine Dopamine
Vesicular acetylcholine transporter	VAChT	SLC18	Acetylcholine
Vesicular inhibitory amino acid transporter	VIAAT	SLC32	GABA
Vesicular glutamate transporters 1–3	VGluT1–3	SLC17	Glutamate

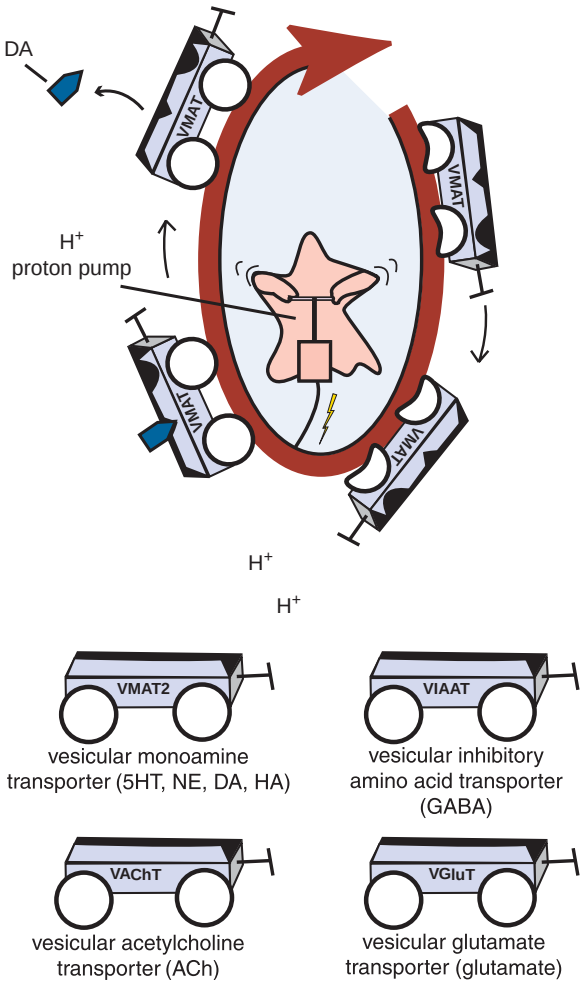


Figure 2-2B. Vesicular transporters. Vesicular transporters package neurotransmitters into synaptic vesicles through the use of a proton ATPase, or proton pump. The proton pump utilizes energy to pump positively charged protons continuously out of the synaptic vesicle. Neurotransmitter can then be transported into the synaptic vesicle, keeping the charge inside the vesicle constant. Examples of vesicular transporters include the vesicular monoamine transporter (VMAT2), which transports serotonin, norepinephrine, dopamine, and histamine; the vesicular acetylcholine transporter (VAChT), which transports acetylcholine; the vesicular inhibitory amino acid transporter (VIAAT), which transports GABA; and the vesicular glutamate transporter (VGluT), which transports glutamate.

Why does this matter? Blocking the presynaptic monoamine transporter has a huge impact on neurotransmission at any synapse that utilizes that neurotransmitter. The normal recapture of neurotransmitter by the presynaptic neurotransmitter transporter in Figure 2-2A keeps the levels of this neurotransmitter from accumulating in the synapse. Normally, following release from the presynaptic neuron, neurotransmitters only have time for a brief dance on their synaptic receptors, and the party is soon over because the monoamines climb back into the presynaptic neuron on their transporters (Figure 2-2A). If one wants to enhance normal synaptic activity of these neurotransmitters, or restore their diminished synaptic activity, this can be accomplished by blocking these transporters. Although this might not seem to be a very dramatic thing, the fact is that this alteration in chemical neurotransmission – namely the enhancement of synaptic monoamine action – is thought to underlie the clinical effects of all the agents that block monoamine transporters, including most known antidepressants and stimulants. Specifically, many antidepressants enhance serotonin, norepinephrine, or both, due to actions on SERT and/or NET. Some antidepressants act on DAT, as do stimulants. Also, recall that many antidepressants that block monoamine transporters are also effective anxiolytics, reduce neuropathic pain, and have additional therapeutic actions as well. Thus, it may come as no surprise that drugs that block monoamine transporters are among the most frequently prescribed psychotropic drugs. In fact, about a third of the currently prescribed essential psychotropic drugs act by targeting one or more of the three monoamine transporters.

Other neurotransmitter transporters (SLC6 and SLC1 gene families) as targets of psychotropic drugs

In addition to the three transporters for monoamines discussed in detail above, there are several other transporters for various different neurotransmitters or their precursors. Although this includes a dozen additional transporters, there is only one psychotropic drug used clinically that is known to bind to any of these transporters. Thus, there is a presynaptic transporter for choline, the precursor to the neurotransmitter acetylcholine, but no known drugs target this transporter. There are also several transporters for the ubiquitous inhibitory neurotransmitter GABA, known as GAT1–4 (Table 2-2). Although debate continues about the exact localization of these subtypes at presynaptic neurons, neighboring glia, or even postsynaptic neurons, it is clear that a key presynaptic transporter of GABA is the GAT1 transporter, which is selectively blocked by the anticonvulsant tiagabine, thereby increasing synaptic GABA concentrations. In addition to anticonvulsant actions, this increase in synaptic GABA may have therapeutic actions in anxiety, sleep disorders, and pain. No other inhibitors of this transporter are available for clinical use.

Finally, there are multiple transporters for two amino acid neurotransmitters, glycine and glutamate (Table 2-2). There are no drugs utilized in clinical practice that are known to block glycine transporters, although new agents are in clinical trials for treating schizophrenia. The glycine transporters, along with the choline and GABA transporters, are all members of the same family to which the monoamine transporters belong and have a similar structure (Figure 2-2A, Tables 2-1 and 2-2). However, the glutamate transporters belong to a unique family, SLC1, and have a unique structure and somewhat different functions compared to those transporters of the SLC6 family (Table 2-2).

Specifically, there are several transporters for glutamate, known as excitatory amino acid transporters 1–5, or EAAT1–5 (Table 2-2). The exact localization of these various transporters at presynaptic neurons, postsynaptic neurons, or glia is still under investigation, but the uptake of glutamate into glia is well known to be a key system for recapturing glutamate for reuse once it has been released. Transport into glia results in conversion of glutamate into glutamine, and then glutamine enters the presynaptic neuron for reconversion back into glutamate. No drugs utilized in clinical practice are known to block glutamate transporters.

One difference between transport of neurotransmitters by the SLC6 gene family and transport of glutamate by the SLC1 gene family is that glutamate does not seem to cotransport chloride with sodium when it also cotransports glutamate. Also, glutamate transport is almost always characterized by the countertransport of potassium, whereas this is not always the case with SLC6 gene family transporters. Glutamate transporters may work together as trimers rather than dimers, as the SLC6 transporters seem to do. The functional significance of these differences remains obscure, but may become more apparent if clinically useful psychopharmacologic agents that target glutamate transporters are discovered. Since it may often be desirable to diminish rather than enhance glutamate neurotransmission, the future utility of glutamate transporters as therapeutic targets is also unclear.

Where are the transporters for histamine and neuropeptides?

It is an interesting observation that apparently not all neurotransmitters are regulated by reuptake transporters. The central neurotransmitter histamine apparently does not have a presynaptic transporter (although it is transported into synaptic vesicles by VMAT2, the same transporter used by the monoamines – see Figure 2-2B). Histamine's inactivation is thus thought to be entirely enzymatic. The same can be said for neuropeptides, since reuptake pumps and presynaptic transporters have not been found for them, and are thus thought to be lacking for this class of neurotransmitter. Inactivation of neuropeptides is apparently by diffusion, sequestration, and enzymatic destruction, but not by presynaptic transport. It is always possible that a transporter will be discovered in the future for some of these neurotransmitters, but at the present time there are no known presynaptic transporters for either histamine or neuropeptides.

Vesicular transporters: subtypes and function

Vesicular transporters for the monoamines (VMATs) are members of the SLC18 gene family and have already been discussed above. They are shown in

Figure 2-2B and listed in Table 2-3, as is the vesicular transporter for acetylcholine – also a member of the SLC18 gene family but known as VAChT. The GABA vesicular transporter is a member of the SLC32 gene family and is called VIAAT (vesicular inhibitory amino acid transporter; Figure 2-2B and Table 2-3). Finally, vesicular transporters for glutamate, called vGluT1–3 (vesicular glutamate transporters 1, 2, and 3) are members of the SLC17 gene family – and are also shown in Figure 2-2B and listed in Table 2-3. The SV2A transporter is a novel twelve-transmembrane-region synaptic vesicle transporter of uncertain mechanism and with unclear substrates; it is localized within the synaptic vesicle membrane and binds the anticonvulsant levetiracetam, perhaps interfering with neurotransmitter release and thereby reducing seizures.

How do neurotransmitters get inside synaptic vesicles? In the case of vesicular transporters, storage of neurotransmitters is facilitated by a proton ATPase, known as the "proton pump," that utilizes energy to pump positively charged protons continuously out of the synaptic vesicle (Figure 2-2B). The neurotransmitters can then be concentrated against a gradient by substituting their own positive charge inside the vesicle for the positive charge of the proton being pumped out. Thus, neurotransmitters are not so much transported as "antiported" – i.e., they go in while the protons are actively transported out, keeping charge inside the vesicle constant. This concept is shown in Figure 2-2B for the VMAT transporting dopamine in exchange for protons. Contrast this with Figure 2-2A, where a monoamine transporter on the presynaptic membrane is cotransporting a monoamine along with sodium and chloride, but with the help of a sodium-potassium ATPase (sodium pump) rather than a proton pump.

Vesicular transporters (SLC18 gene family) as targets of psychotropic drugs

Vesicular transporters for acetylcholine (SLC18 gene family), GABA (SLC32 gene family), and glutamate (SLC17 gene family) are not known to be targeted by any drug utilized by humans. However, vesicular transporters for monoamines in the SLC18 gene family, or VMATs, particularly those in dopamine and norepinephrine neurons, are potently targeted by several drugs including amphetamine, tetrabenazine, and reserpine. Amphetamine thus has two targets: monoamine transporters as well as VMATs. In contrast, other stimulants such as methylphenidate and cocaine target only the monoamine transporters, and in much the same manner as described for antidepressants (see Chapter 7).

G-protein-linked receptors

Structure and function

Another major target of psychotropic drugs is the class of receptors linked to G proteins. These receptors all have the structure of seven transmembrane regions, meaning that they span the membrane seven times (Figure 2-1). Each of the transmembrane regions clusters around a central core that contains a binding site for a neurotransmitter. Drugs can interact at this neurotransmitter binding site or at other sites (allosteric sites) on the receptor. This can lead to a wide range of modifications of receptor actions due to mimicking or blocking, partially or fully, the neurotransmitter function that normally occurs at this receptor. These drug actions can thus change downstream molecular events such as which phosphoproteins are activated or inactivated and therefore which enzymes, receptors, or ion channels are modified by neurotransmission. Such drug actions can also change which genes are expressed, and thus which proteins are synthesized and which functions are amplified, from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the G-protein-linked receptor.

These actions on neurotransmission by G-protein-linked receptors are described in detail in Chapter 1 on signal transduction and chemical neurotransmission. The reader should have a good command of the function of G-protein-linked receptors and their role in signal transduction from specific neurotransmitters, as described in Chapter 1, in order to understand how drugs acting at G-protein-linked receptors modify the signal transduction that arises from these receptors. This is important to understand because such drug-induced modifications in signal transduction from G-protein-linked receptors can have profound actions on psychiatric symptoms. In fact, the single most common action of psychotropic drugs utilized in clinical practice is to modify the actions of G-protein-linked receptors, resulting in either therapeutic actions or side effects. Here we will describe how

various drugs stimulate or block these receptors, and throughout the textbook we will show how specific drugs acting at specific G-protein-linked receptors have specific actions on specific psychiatric disorders.

G-protein-linked receptors as targets of psychotropic drugs

G-protein-linked receptors are a large superfamily of receptors that interact with many neurotransmitters and with many psychotropic drugs (Figure 2-1B). There are numerous ways to subtype these receptors, but pharmacologic subtypes are perhaps the most important to understand for clinicians who wish to target specific receptors with psychotropic drugs utilized in clinical practice. That is, the natural neurotransmitter interacts at all of its receptor subtypes, but many drugs are more selective than the neurotransmitter itself for certain receptor subtypes and thus define a pharmacologic subtype of receptor at which they specifically interact. This is not unlike the concept of the neurotransmitter being a master key that opens all the doors, and a drug that interacts at pharmacologically specific receptor subtypes functioning as a specific key opening only one door. Here we will develop the concept that drugs have many different ways of interacting at pharmacologic subtypes of G-protein-linked receptors, which occur across an agonist spectrum (Figure 2-3).

No agonist

An important concept for the agonist spectrum is that the absence of agonist does not necessarily mean that nothing is happening with signal transduction at G-protein-linked receptors. Agonists are thought to produce a conformational change in G-protein-linked receptors that leads to full receptor activation, and thus full signal transduction. In the absence of agonist, this same conformational change may still be occurring at some receptor systems, but only at very low frequency. This is referred to as *constitutive activity*, which may be present especially in receptor systems and brain areas where there is a high density of receptors. Thus, when something occurs at very low frequency but among a high number of receptors, it can still produce detectable signal transduction output. This is represented as a small – but not absent – amount of signal transduction in Figure 2-4.

Agonists

An agonist produces a conformational change in the G-protein-linked receptor that turns on the synthesis of second messenger to the greatest extent possible (i.e., the action of a *full agonist*). The full agonist is generally represented by the naturally occurring neurotransmitter itself, although some drugs can also act in as full a manner as the natural neurotransmitter. What this means from the perspective of chemical neurotransmission is that the full array of downstream signal transduction is triggered by a full

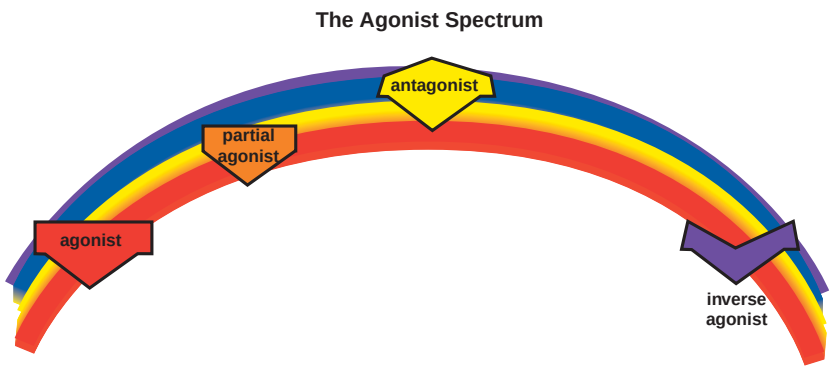


Figure 2-3. Agonist spectrum. Shown here is the agonist spectrum. Naturally occurring neurotransmitters stimulate receptors and are thus agonists. Some drugs also stimulate receptors and are therefore agonists as well. It is possible for drugs to stimulate receptors to a lesser degree than the natural neurotransmitter; these are called partial agonists or stabilizers. It is a common misconception that antagonists are the opposite of agonists because they block the actions of agonists. However, although antagonists prevent the actions of agonists, they have no activity of their own in the absence of the agonist. For this reason, antagonists are sometimes called "silent." Inverse agonists, on the other hand, do have opposite actions compared to agonists. That is, they not only block agonists but can also reduce activity below the baseline level when no agonist is present. Thus, the agonist spectrum reaches from full agonists to partial agonists through to "silent" antagonists and finally inverse agonists.

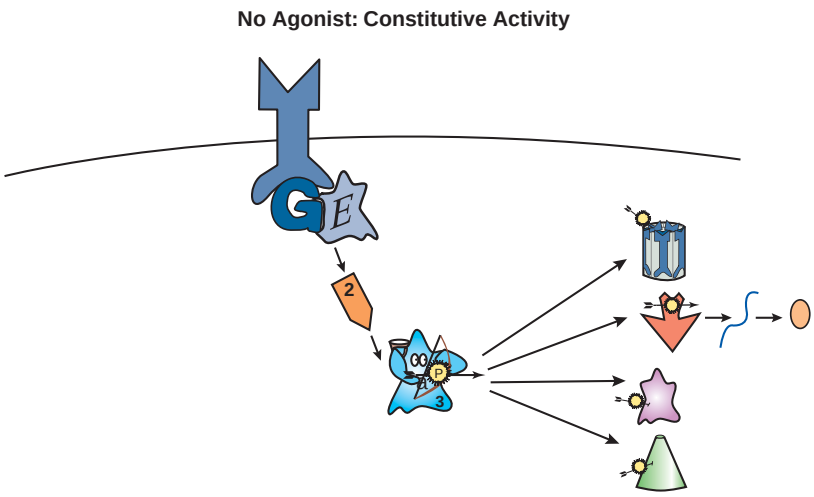


Figure 2-4. Constitutive activity. The absence of agonist does not mean that there is no activity related to G-protein-linked receptors. Rather, in the absence of agonist, the receptor's conformation is such that it leads to a low level of activity, or constitutive activity. Thus, signal transduction still occurs, but at a low frequency. Whether this constitutive activity leads to detectable signal transduction is affected by the receptor density in that brain region.

agonist (Figure 2-5). Thus, downstream proteins are maximally phosphorylated, and genes are maximally impacted. Loss of the agonist actions of a neurotransmitter at G-protein-linked receptors, due to deficient neurotransmission of any cause, would lead to the loss of this rich downstream chemical tour de force. Thus, agonists that restore this natural action would be potentially useful in states where reduced signal transduction leads to undesirable symptoms.

There are two major ways to stimulate G-protein-linked receptors with full agonist action. First, several drugs *directly* bind to the neurotransmitter site and produce the same array of signal transduction effects as a full agonist (Table 2-4). These are direct-acting agonists. Second, many drugs can *indirectly* act to boost the levels of the natural full agonist neurotransmitter (Table 2-5). This happens when neurotransmitter inactivation mechanisms are blocked. The most prominent examples of indirect full agonist actions have already been discussed above, namely inhibition of the monoamine transporters SERT, NET, and DAT and the GABA transporter GAT1. Another way to accomplish indirect full agonist action is to block the enzymatic destruction of neurotransmitters (Table 2-5). Two examples of this are inhibition of the enzymes monoamine oxidase (MAO) and acetylcholinesterase.

Antagonists

On the other hand, it is also possible that full agonist action can be too much of a good thing and that maximal activation of the signal transduction cascade is not always desirable, as in states of overstimulation by neurotransmitters. In such cases, blocking the action of the natural neurotransmitter agonist may be desirable. This is the property of an antagonist. Antagonists produce a conformational change in the G-protein-linked receptor that causes no change in signal transduction – including no change in whatever amount of any constitutive activity that may have been present in the absence of agonist (compare Figure 2-4 with Figure 2-6). Thus, true antagonists are "neutral" and, since they have no actions of their own, are also called "silent."

There are many more examples in clinical practice of important antagonists of G-protein-linked receptors than there are of direct-acting full agonists (Table 2-4). Antagonists are well known both as the mediators of therapeutic actions in psychiatric disorders and as the cause of undesirable side effects (Table 2-4). Some of these may prove to be inverse agonists (see below), but most antagonists utilized in clinical practice are characterized simply as "antagonists."

Antagonists block the actions of everything in the agonist spectrum (Figure 2-3). In the presence of an agonist, an antagonist will block the actions of that agonist but does nothing itself (Figure 2-6). The antagonist simply returns the receptor conformation back to the same state as exists when no agonist is present (Figure 2-4). Interestingly, an antagonist will also block the actions of a partial agonist. Partial agonists are thought to produce a conformational change in the G-protein-linked receptor that is intermediate between a full agonist and the baseline conformation of the receptor in the absence of

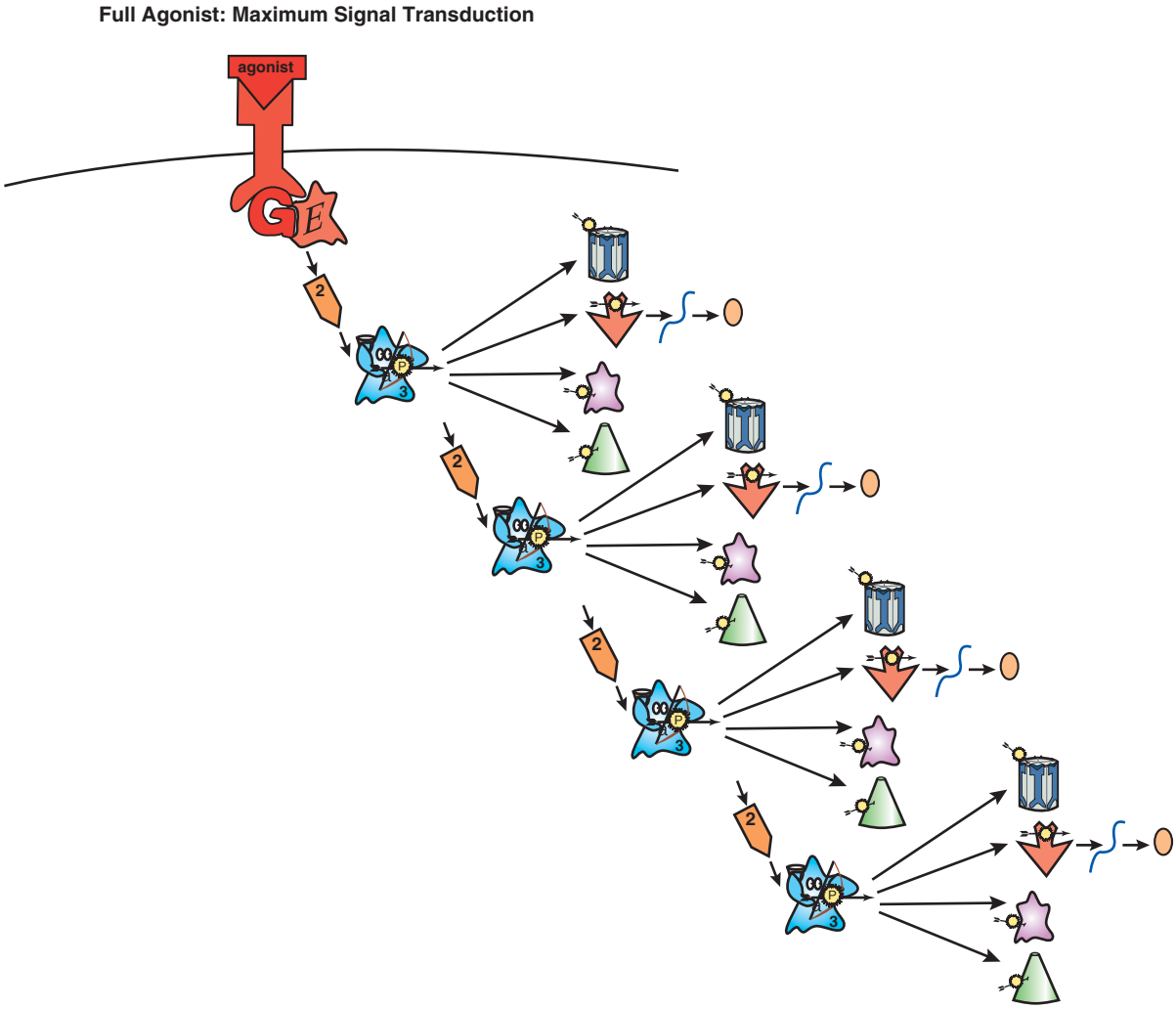


Figure 2-5. Full agonist: maximum signal transduction. When a full agonist binds to G-protein-linked receptors, it causes conformational changes that lead to maximum signal transduction. Thus, all the downstream effects of signal transduction, such as phosphorylation of proteins and gene activation, are maximized.

agonist (Figures 2-7 and 2-8). An antagonist reverses the action of a partial agonist by returning the G-protein-linked receptor to the same conformation (Figure 2-6) as exists when no agonist is present (Figure 2-4). Finally, an antagonist reverses an inverse agonist. Inverse agonists are thought to produce a conformational state of the receptor that totally inactivates it and even removes the baseline constitutive activity (Figure 2-9). An antagonist reverses this back to the baseline state that allows constitutive activity (Figure 2-6), the same as exists for the receptor in the absence of the neurotransmitter agonist (Figure 2-4).

By themselves, therefore, it is easy to see that true antagonists have no activity, and why they are sometimes referred to as "silent." Silent antagonists return the entire spectrum of drug-induced conformational changes in the G-protein-linked receptor (Figures 2-3 and 2-10) to the same place (Figure 2-6) – i.e., the conformation that exists in the absence of agonist (Figure 2-4).

Partial agonists

It is possible to produce signal transduction that is something more than an antagonist yet something less than a full agonist. Turning down the gain a bit

Table 2-4 Key G-protein-linked receptors directly targeted by psychotropic drugs

Neurotransmitter	G-protein receptor and pharmacologic subtype directly targeted	Pharmacologic action	Drug class	Therapeutic action
Dopamine	D_2	Antagonist or partial agonist	Conventional antipsychotic; atypical antipsychotic	Antipsychotic; antimanic
Serotonin	$5HT_{2A}$	Antagonist or inverse agonist	Atypical antipsychotic	Reduced motor side effects; possible mood stabilizing and antidepressant actions in bipolar disorder
			Antidepressant, hypnotic	Improve mood and insomnia
	$5HT_{1A}$ $5HT_{1B/D}$ $5HT_{2C}$ $5HT_6$ $5HT_7$	Antagonist or partial agonist	Atypical antipsychotic	Unknown secondary receptor actions, possibly contributing to efficacy and tolerability
	$5HT_{1A}$	Partial agonist	Anxiolytic	Anxiolytic; booster of antidepressant action
Norepinephrine	$Alpha_2$	Antagonist Agonist	Antidepressant Antihypertensive	Antidepressant Cognition and behavioral disturbance in attention deficit hyperactivity disorder
	$Alpha_1$	Antagonist	Many antipsychotics and antidepressants	Side effects of orthostatic hypotension and possibly sedation
GABA	$GABA_B$	Agonist	Gamma hydroxybutyrate/ sodium oxybate	Cataplexy, sleepiness in narcolepsy; possible enhanced slow-wave sleep and pain reduction
Melatonin	MT_1 MT_2	Agonist Agonist	Hypnotic Hypnotic	Improve insomnia Improve insomnia
Histamine	H_1	Antagonist	Many antipsychotics and antidepressants; some anxiolytics	Therapeutic effect for anxiety and insomnia; side effect of sedation and weight gain
Acetylcholine	M_1	Antagonist	Many antipsychotics and antidepressants	Side effects of memory disturbance, sedation, dry mouth, blurred vision, constipation, urinary retention
	M_3/M_5	Antagonist	Some atypical antipsychotics	May contribute to metabolic dysregulation (dyslipidemia and diabetes)

Table 2-5 Key G-protein-linked receptors indirectly targeted by psychotropic drugs

Neurotransmitter	G-protein receptor and pharmacologic subtype indirectly targeted	Pharmacologic action	Drug class	Therapeutic action
Dopamine	D_1 and D_2 (possibly D_3, D_4)	Agonist via increasing dopamine itself at all dopamine receptors	Stimulant (actions at dopamine and/or synaptic vesicle transporters DAT and VMAT2)	Improvement of attention deficit hyperactivity disorder (ADHD)
			Antidepressant (actions at dopamine and/or norepinephrine transporters DAT and/or NET)	Antidepressant; ADHD
			MAO inhibitor (reducing dopamine metabolism)	Antidepressant
Serotonin	$5HT_{1A}$ (presynaptic somadendritic autoreceptors)	Agonist via increasing serotonin itself at all serotonin receptors	Antidepressant (actions at serotonin transporters SERT)	Antidepressant; anxiolytic
	$5HT_{2A}$ postsynaptic receptors; possibly $5HT_{1A}$, $5HT_{2C}$, $5HT_6$, $5HT_7$ postsynaptic receptors			
			MAO inhibitor (reducing serotonin metabolism)	Antidepressant
Norepinephrine	$Beta_2$ postsynaptic; possibly $alpha_2$ presynaptic and postsynaptic	Agonist via increasing norepinephrine itself at all norepinephrine receptors	Antidepressant; neuropathic pain (actions at norepinephrine transporter NET)	Antidepressant; improve ADHD; for chronic pain (when combined with SERT inhibition)
			MAO inhibitor (reducing norepinephrine metabolism)	Antidepressant
GABA	$GABA_A$ and $GABA_B$	Agonist via increasing GABA itself at all GABA receptors	Anticonvulsant (actions at the GABA GAT1 transporter)	Anticonvulsant; possibly anxiolytic, for chronic pain, for slow-wave sleep
Acetylcholine	M_1 (possibly M_2–M_5)	Agonist via increasing acetylcholine itself at all acetylcholine receptors	Acetylcholinesterase inhibitor (reducing acetylcholine metabolism)	Slowing progression in Alzheimer's disease

DAT, dopamine transporter; MAO, monoamine oxidase; NET, norepinephrine transporter; SERT, serotonin transporter; VMAT, vesicular monoamine transporter.

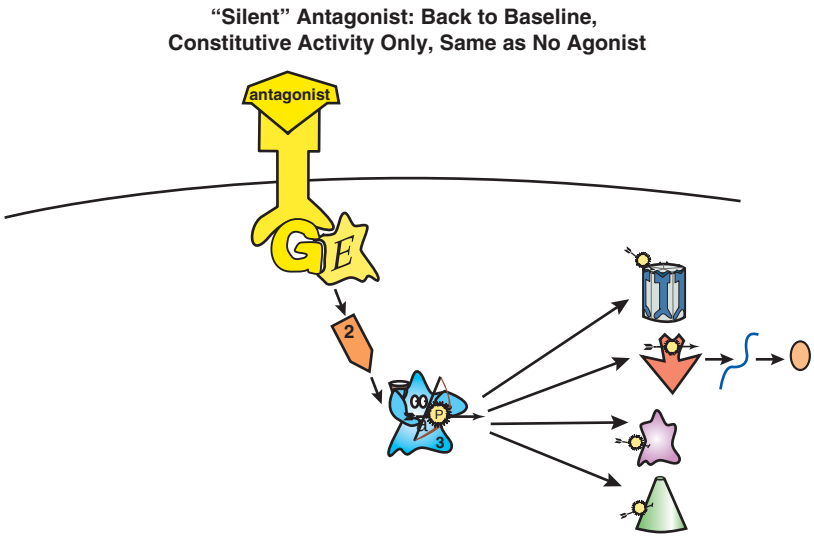


Figure 2-6. "Silent" antagonist. An antagonist blocks agonists (both full and partial) from binding to G-protein-linked receptors, thus preventing agonists from causing maximum signal transduction and instead changing the receptor's conformation back to the same state as exists when no agonist is present. Antagonists also reverse the effects of inverse agonists, again by blocking the inverse agonists from binding and then returning the receptor conformation to the baseline state. Antagonists do not have any impact on signal transduction in the absence of an agonist.

from full agonist actions, but not all the way to zero, is the property of a partial agonist (Figure 2-7). This action can also be seen as turning up the gain a bit from silent antagonist actions, but not all the way to a full agonist. Depending upon how close this partial agonist is to a full agonist or to a silent antagonist on the agonist spectrum will determine the impact of a partial agonist on downstream signal transduction events.

The amount of "partiality" that is desired between agonist and antagonist – that is, where a partial agonist should sit on the agonist spectrum – is a matter of debate as well as trial and error. The ideal therapeutic agent may have signal transduction through G-protein-linked receptors that is not too "hot," yet not too "cold," but "just right," sometimes called the "Goldilocks" solution. Such an ideal state may vary from one clinical situation to another, depending upon the balance between full agonism and silent antagonism that is desired.

In cases where there is unstable neurotransmission throughout the brain, such as when pyramidal neurons in the prefrontal cortex are out of "tune," it may be desirable to find a state of signal transduction that stabilizes G-protein-linked receptor output somewhere between too much and too little downstream action. For this reason, partial agonists are also called "stabilizers," since they have the theoretical capacity to find a stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 2-7).

Since partial agonists exert an effect less than that of a full agonist, they are also sometimes called "weak," with the implication that partial agonism means partial clinical efficacy. That is certainly possible in some cases, but it is more sophisticated to understand the potential stabilizing and "tuning" actions of this class of therapeutic agents, and not to use terms that imply clinical actions for the entire class of drugs that may only apply to some individual agents. A few partial agonists are utilized in clinical practice (Table 2-4) and more are in clinical development.

Light and dark as an analogy for partial agonists

It was originally conceived that a neurotransmitter could only act at receptors like a light switch, turning things on when the neurotransmitter is present and turning things off when the neurotransmitter is absent. We now know that many receptors, including the G-protein-linked receptor family, can function rather more like a rheostat. That is, a full agonist will turn the lights all the way on (Figure 2-8A), but a partial agonist will only turn the light on partially (Figure 2-8B). If neither full agonist nor partial agonist is present, the room is dark (Figure 2-8C).

Each partial agonist has its own set point engineered into the molecule, such that it cannot turn the lights on brighter even with a higher dose. No matter how much partial agonist is given, only a certain degree of brightness will result. A series of partial agonists will differ one from the other in the degree

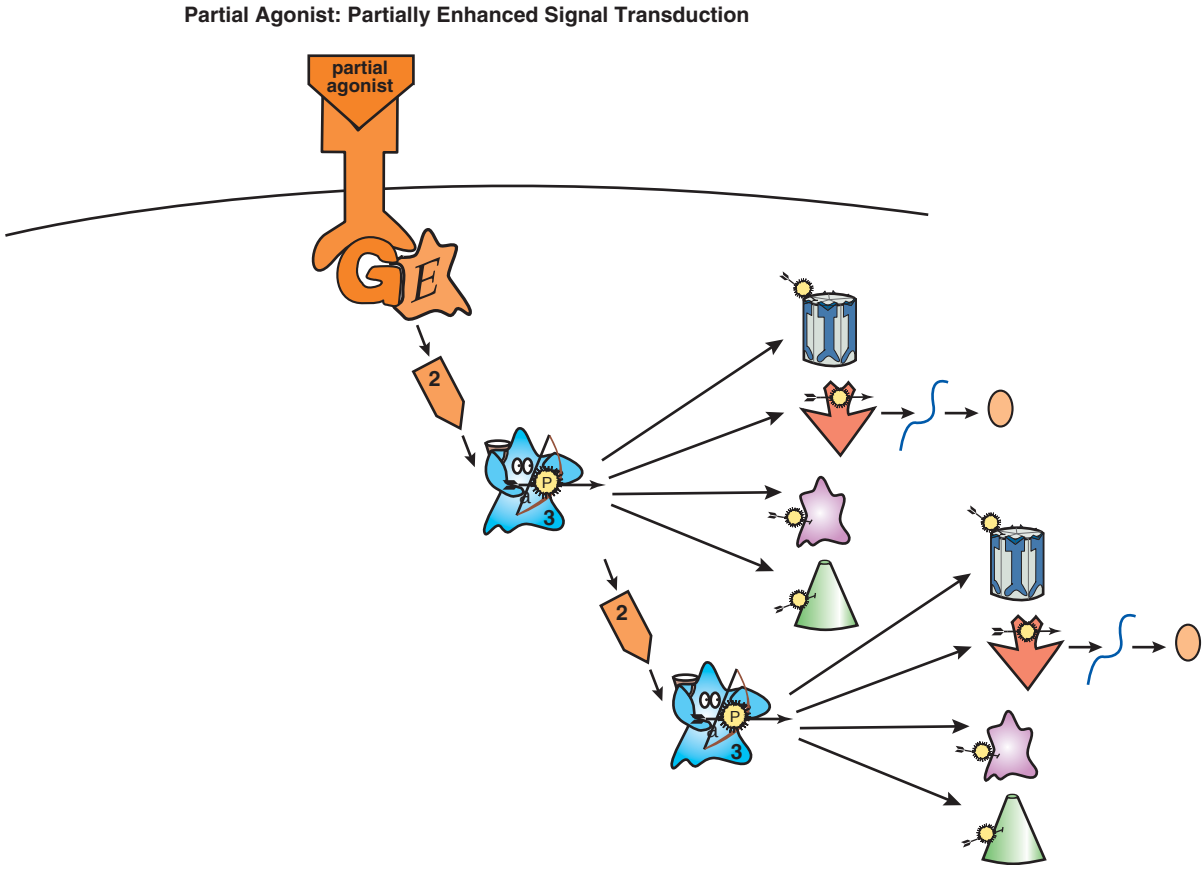


Figure 2-7. Partial agonist. Partial agonists stimulate G-protein-linked receptors to enhance signal transduction but do not lead to maximum signal transduction the way full agonists do. Thus, in the absence of a full agonist, partial agonists increase signal transduction. However, in the presence of a full agonist, the partial agonist will actually turn down the strength of various downstream signals. For this reason, partial agonists are sometimes referred to as stabilizers.

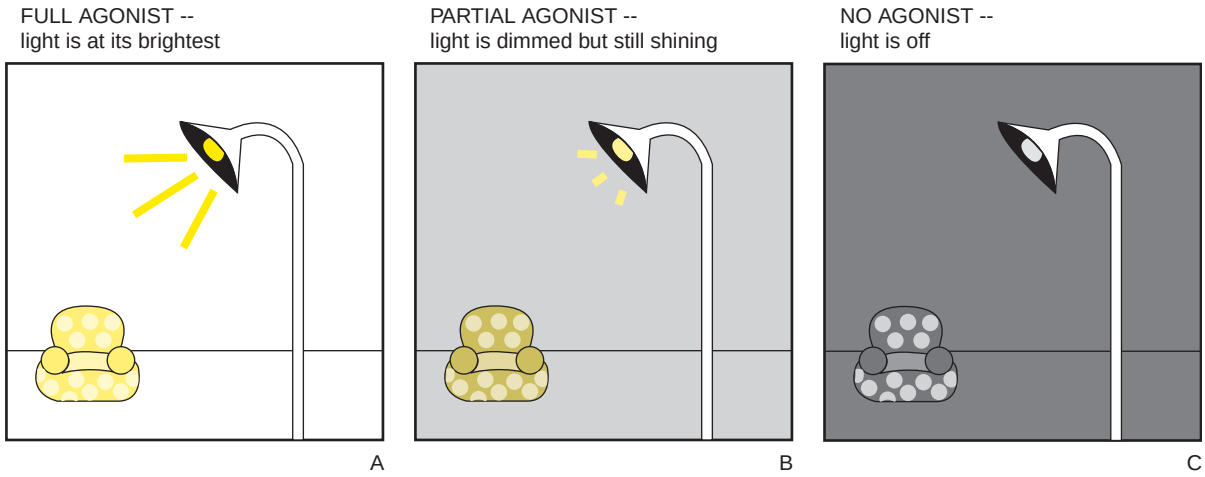


Figure 2-8. Agonist spectrum: rheostat. A useful analogy for the agonist spectrum is a light controlled by a rheostat. The light will be brightest after a full agonist turns the light switch fully on (A). A partial agonist will also act as a net agonist and turn the light on, but only partially, according to the level preset in the partial agonist's rheostat (B). If the light is already on, a partial agonist will "dim" the lights, thus acting as a net antagonist. When no full or partial agonist is present, the situation is analogous to the light being switched off (C).

of partiality, so that theoretically all degrees of brightness can be covered within the range from "off" to "on," but each partial agonist has its own unique degree of brightness associated with it.

What is so interesting about partial agonists is that they can appear as a net agonist, or as a net antagonist, depending upon the amount of naturally occurring full agonist neurotransmitter that is present. Thus, when a full agonist neurotransmitter is absent, a partial agonist will be a net agonist. That is, from the resting state, a partial agonist initiates somewhat of an increase in the signal transduction cascade from the G-protein-linked second-messenger system. However, when full agonist neurotransmitter is present, the same partial agonist will become a net antagonist. That is, it will decrease the level of full signal output to a lesser level, but not to zero. Thus, a partial agonist can simultaneously *boost* deficient neurotransmitter activity yet *block* excessive neurotransmitter activity, another reason that partial agonists are called stabilizers.

Returning to the light-switch analogy, a room will be dark when agonist is missing and the light switch is off (Figure 2-8C). A room will be brightly lit when it is full of natural full agonist and the light switch is fully on (Figure 2-8A). Adding partial agonist to the dark room where there is no natural full agonist neurotransmitter will turn the lights up, but only as far as the partial agonist works on the rheostat (Figure 2-8B). Relative to the dark room as a starting point, a partial agonist acts therefore as a net agonist. On the other hand, adding a partial agonist to the fully lit room will have the effect of turning the lights down to the intermediate level of lower brightness on the rheostat (Figure 2-8B). This is a net antagonistic effect relative to the fully lit room. Thus, after adding partial agonist to the dark room and to the brightly lit room, both rooms will be equally light. The degree of brightness is that of being partially turned on, as dictated by the properties of the partial agonist. However, in the dark room, the partial agonist has acted as a net agonist, whereas in the brightly lit room, the partial agonist has acted as a net antagonist.

An agonist and an antagonist in the same molecule is quite a new dimension to therapeutics. This concept has led to proposals that partial agonists could treat not only states that are theoretically deficient in full agonist, but also those that have a theoretical excess of full agonist. A partial agonist may even be able to treat simultaneously states that are mixtures of both excess and deficiency in neurotransmitter activity.

Figure 2-9. Inverse agonist. Inverse agonists produce conformational change in the G-protein-linked receptor that renders it inactive. This leads to reduced signal transduction as compared not only to that associated with agonists but also to that associated with antagonists or the absence of an agonist. The impact of an inverse agonist is dependent on the receptor density in that brain region. That is, if the receptor density is so low that constitutive activity does not lead to detectable signal transduction, then reducing the constitutive activity would not have any appreciable effect.

Inverse agonists

Inverse agonists are more than simple antagonists, and are neither neutral nor silent. These agents have an action that is thought to produce a conformational change in the G-protein-linked receptor that stabilizes it in a totally inactive form (Figure 2-9). Thus, this conformation produces a functional reduction in signal transduction (Figure 2-9) that is even less than that produced when there is either no agonist present (Figure 2-4) or a silent antagonist present (Figure 2-6). The result of an inverse agonist is to shut down even the constitutive activity of the G-protein-linked receptor system. Of course, if a given receptor system has no constitutive activity, perhaps in cases when receptors are present in low density, then there will be no reduction in activity and the inverse agonist will look like an antagonist.

In many ways, therefore, inverse agonists do the *opposite* of agonists. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. In contrast to agonists and antagonists, therefore, an *inverse agonist* neither increases signal transduction like an agonist (Figure 2-5) nor merely blocks the agonist from increasing signal transduction like an antagonist (Figure 2-6); rather, an inverse agonist binds the receptor in a fashion so as to provoke an action opposite to that of the agonist, namely causing the receptor to *decrease* its baseline signal transduction level (Figure 2-9). It is unclear from a clinical point of view what the relevant differences are between an inverse agonist and a silent antagonist. In fact, some drugs that have long been considered to be silent antagonists may turn out in some areas of the brain to be

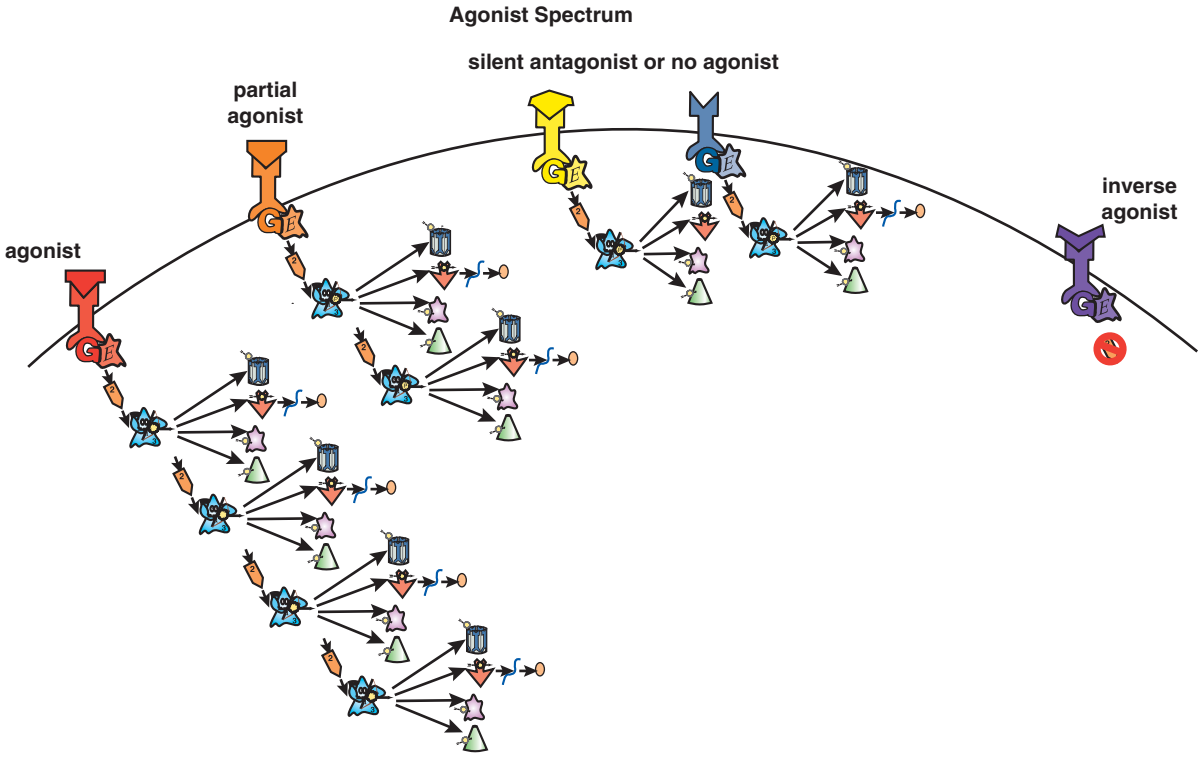


Figure 2-10. Agonist spectrum. This figure summarizes the implications of the agonist spectrum. Full agonists cause maximum signal transduction, while partial agonists increase signal transduction compared to no agonist but decrease it compared to full agonist. Antagonists allow constitutive activity and thus, in the absence of an agonist, have no effects themselves; in the presence of an agonist, antagonists lead to reduced signal transduction. Inverse agonists are the functional opposites of agonists and actually reduce signal transduction beyond that produced in the absence of an agonist.

inverse agonists. Thus, the concept of an inverse agonist as clinically distinguishable from a silent antagonist remains to be proven. In the meantime, inverse agonists remain an interesting pharmacological concept.

In summary, G-protein-linked receptors act along an agonist spectrum, and drugs have been described that can produce conformational changes in these receptors to create any state from full agonist, to partial agonist, to silent antagonist, to inverse agonist (Figure 2-10). When one considers signal transduction along this spectrum (Figure 2-10), it is easy to understand why agents at each point along the agonist spectrum differ so much from each other, and why their clinical actions are so different.

Enzymes as targets of psychotropic drugs

Enzymes are involved in multiple aspects of chemical neurotransmission, as discussed extensively in Chapter 1 on signal transduction. Every enzyme is the theoretical target for a drug acting as an enzyme inhibitor. However, in practice, only a minority of currently known drugs utilized in the clinical practice of psychopharmacology are enzyme inhibitors.

Enzyme activity is the conversion of one molecule into another, namely a substrate into a product (Figure 2-11). The substrates for each enzyme are unique and selective, as are the products. A substrate (Figure 2-11A) comes to the enzyme to bind at the enzyme's active site (Figure 2-11B), and departs as a changed molecular entity called the product (Figure 2-11C). The inhibitors of an enzyme are also unique and selective for one enzyme compared to another. In the presence of an enzyme inhibitor, the enzyme cannot bind to its substrates. The binding of inhibitors can be either irreversible (Figure 2-12) or reversible (Figure 2-13).

When an irreversible inhibitor binds to the enzyme, it cannot be displaced by the substrate; thus, that inhibitor binds irreversibly (Figure 2-12). This is depicted as binding with chains (Figure 2-12A) that cannot be cut with scissors by the substrate (Figure 2-12B). The irreversible type of enzyme inhibitor is sometimes called a

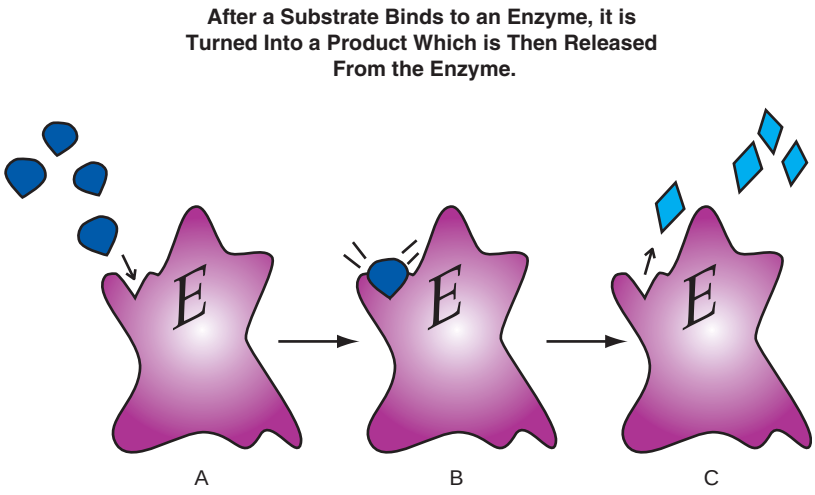


Figure 2-11. Enzyme activity. Enzyme activity is the conversion of one molecule into another. Thus, a substrate is said to be turned into a product by enzymatic modification of the substrate molecule. The enzyme has an active site at which the substrate can bind specifically (A). The substrate then finds the active site of the enzyme and binds to it (B), so that a molecular transformation can occur, changing the substrate into the product (C).

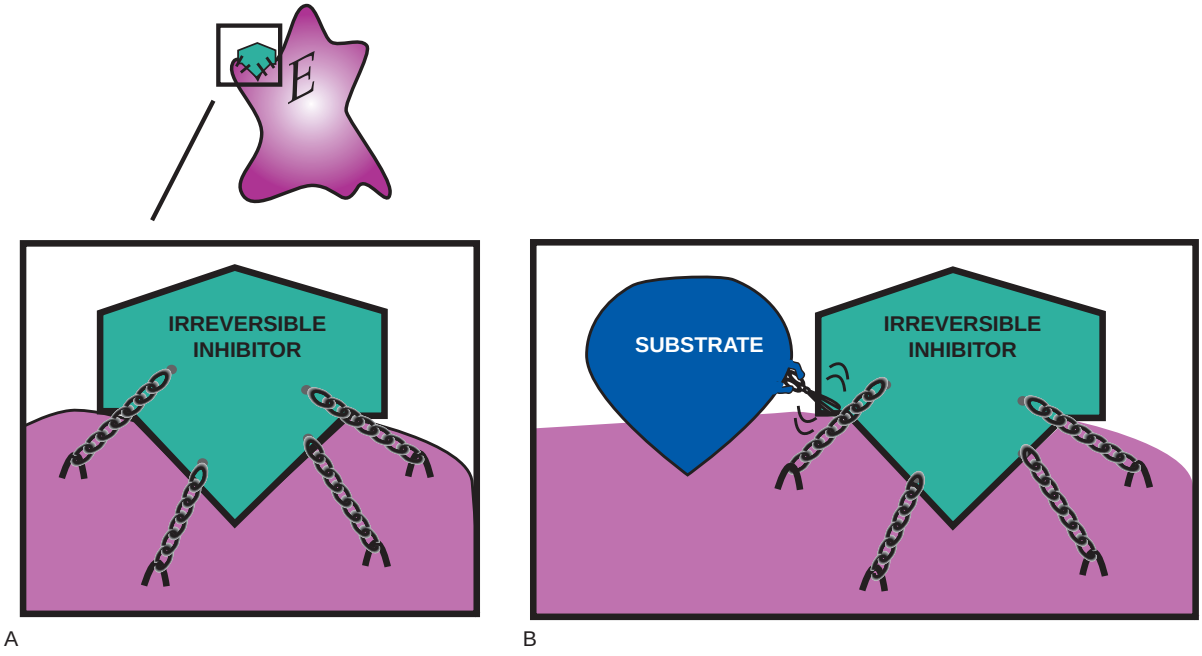


Figure 2-12. Irreversible enzyme inhibitors. Some drugs are inhibitors of enzymes. Shown here is an irreversible inhibitor of an enzyme, depicted as binding to the enzyme with chains (A). A competing substrate cannot remove an irreversible inhibitor from the enzyme, depicted as scissors unsuccessfully attempting to cut the chains off the inhibitor (B). The binding is locked so permanently that such irreversible enzyme inhibition is sometimes called the work of a "suicide inhibitor," since the enzyme essentially commits suicide by binding to the irreversible inhibitor. Enzyme activity cannot be restored unless another molecule of enzyme is synthesized by the cell's DNA.

"suicide inhibitor" because it covalently and irreversibly binds to the enzyme protein, permanently inhibiting it and therefore essentially "killing" it by making the enzyme nonfunctional forever (Figure 2-12). Enzyme activity in this case is only restored when new enzyme molecules are synthesized.

However, in the case of reversible enzyme inhibitors, an enzyme's substrate is able to compete with

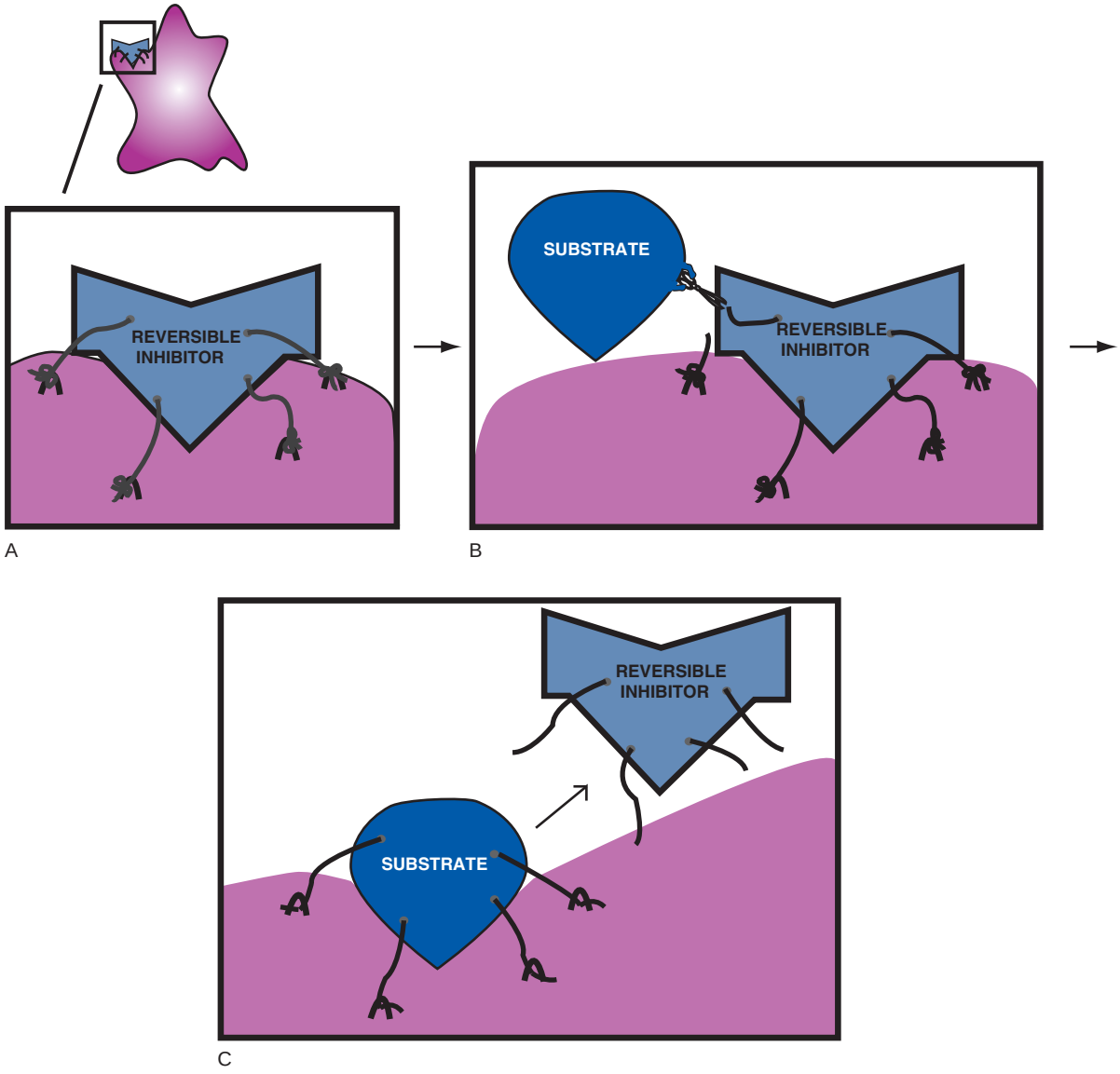


Figure 2-13. Reversible enzyme inhibitors. Other drugs are reversible enzyme inhibitors, depicted as binding to the enzyme with a string (A). A reversible inhibitor can be challenged by a competing substrate for the same enzyme. In the case of a reversible inhibitor, the molecular properties of the substrate are such that it can get rid of the reversible inhibitor, depicted as scissors cutting the string that binds the reversible inhibitor to the enzyme (B). The consequence of a substrate competing successfully for reversal of enzyme inhibition is that the substrate displaces the inhibitor and shoves it off (C). Because the substrate has this capability, the inhibition is said to be reversible.

that reversible inhibitor for binding to the enzyme, and shove it off the enzyme (Figure 2-13). Whether the substrate or the inhibitor "wins" or predominates depends upon which one has the greater affinity for the enzyme and/or is present in the greater concentration. Such binding is called "reversible." Reversible enzyme inhibition is depicted as binding with strings (Figure 2-13A), such that the substrate can cut them with scissors (Figure 2-13B) and displace the enzyme inhibitor, then bind the enzyme itself with its own strings (Figure 2-13C).

These concepts can be applied potentially to any enzyme system. Several enzymes are involved in neurotransmission, including in the synthesis and destruction of neurotransmitters as well as in signal transduction. Only three enzymes are known to be targeted by

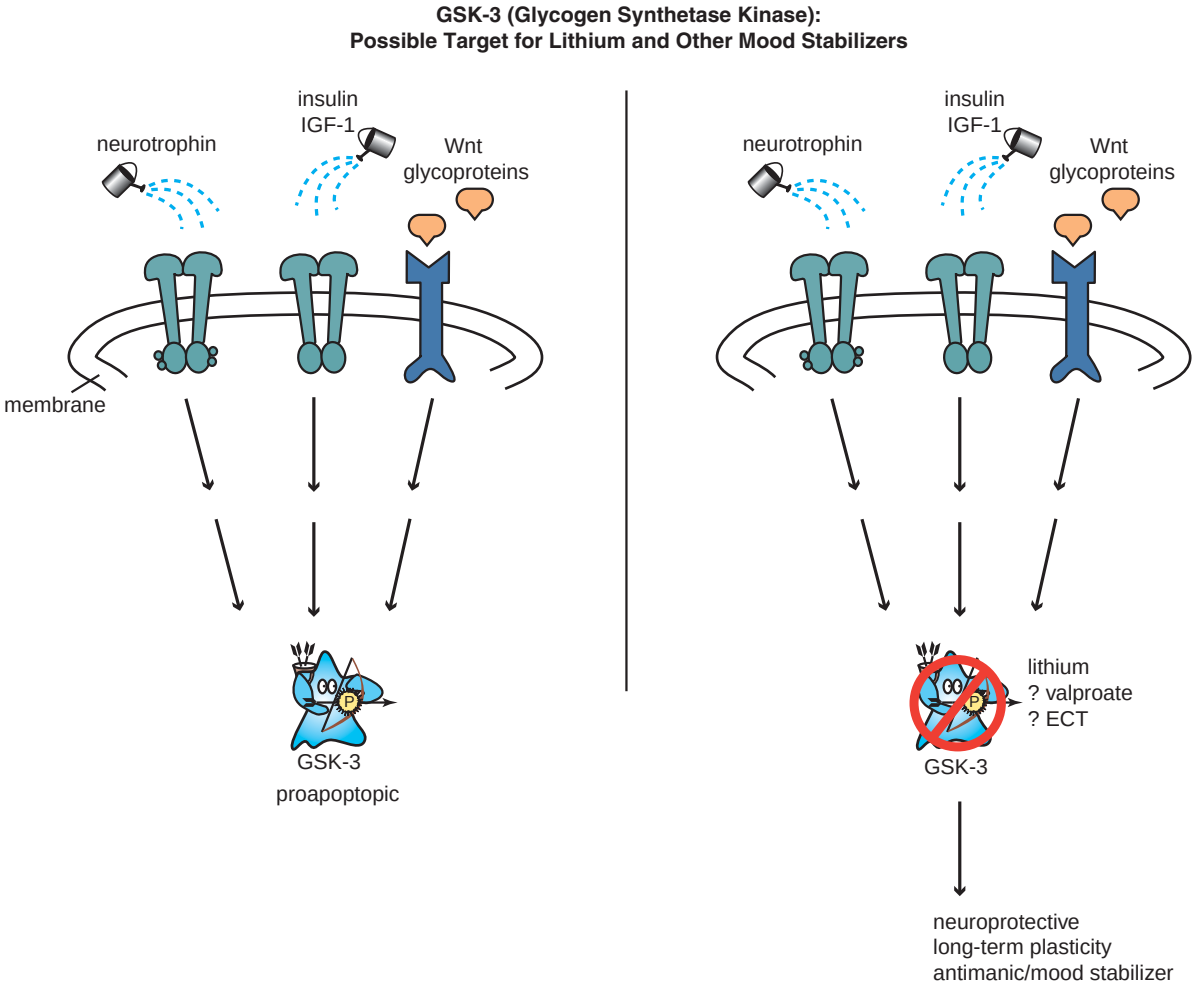


Figure 2-14. Receptor tyrosine kinases. Receptor tyrosine kinases are potential targets for novel psychotropic drugs. Left: Some neurotrophins, growth factors, and other signaling pathways act through a downstream phosphoprotein, an enzyme called GSK-3 (glycogen synthase kinase), to promote cell death (proapoptotic actions). Right: Lithium and possibly some other mood stabilizers may inhibit this enzyme, which could lead to neuroprotective actions and long-term plasticity as well as possibly contribute to mood-stabilizing actions.

psychotropic drugs currently used in clinical practice, namely monoamine oxidase (MAO), acetylcholinesterase, and glycogen synthase kinase (GSK). MAO inhibitors are discussed in more detail in Chapter 7 on antidepressants, and acetylcholinesterase inhibitors are discussed in more detail in Chapter 13 on cognition. Lithium may target an important enzyme in the signal transduction pathway of neurotrophic factors (Figure 2-14). That is, some neurotrophins, growth factors, and other signaling pathways act through a specific downstream phosphoprotein, an enzyme called GSK-3, to promote cell death (proapoptotic actions). Lithium has the capacity to inhibit this enzyme (Figure 2-14). It is possible that inhibition of this enzyme is physiologically relevant, because this action could lead to neuroprotective actions and long-term plasticity and may contribute to the antimanic and mood-stabilizing actions known to be associated with lithium. The development of novel GSK-3 inhibitors is in progress.

Cytochrome P450 drug metabolizing enzymes as targets of psychotropic drugs

Pharmacokinetic actions are mediated through the hepatic and gut drug metabolizing system known as the cytochrome P450 (CYP) enzyme system. **Pharmacokinetics** is the study of how the body acts upon

drugs, especially to absorb, distribute, metabolize, and excrete them. The CYP enzymes and the pharmacokinetic actions they represent must be contrasted with the **pharmacodynamic** actions of drugs, the latter being the major emphasis of this book. Pharmacodynamic actions account for the therapeutic effects and side effects of drugs. However, many psychotropic drugs also target the CYP drug metabolizing enzymes, and a brief overview of these enzymes and their interactions with psychotropic drugs is in order.

CYP enzymes follow the same principles of enzymes transforming substrates into products as illustrated in Figures 2-11 through 2-13. Figure 2-15 depicts the concept of a psychotropic drug being absorbed through the gut wall on the left and then sent to the big blue enzyme in the liver to be biotransformed so that the drug can be sent back into the bloodstream to be excreted from the body via the kidney. Specifically, CYP enzymes in the gut wall or liver convert the drug substrate into a biotransformed product in the bloodstream. After passing through the gut wall and liver, the drug will exist partially as unchanged drug and partially as biotransformed product in the bloodstream (Figure 2-15).

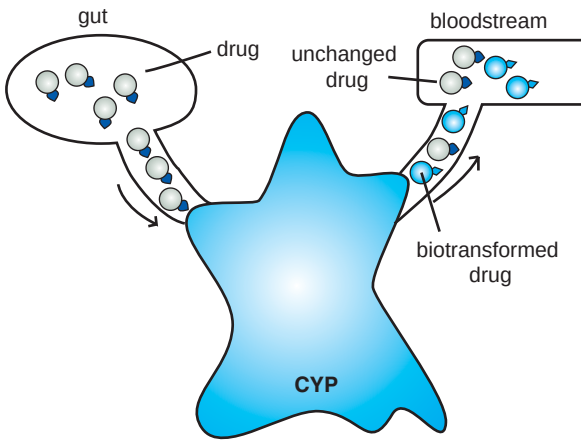


Figure 2-15. Cytochrome P450. The cytochrome P450 (CYP) enzyme system mediates how the body metabolizes many drugs, including antipsychotics. The CYP enzyme in the gut wall or liver converts the drug into a biotransformed product in the bloodstream. After passing through the gut wall and liver (left), the drug will exist partly as unchanged drug and partly as biotransformed drug (right).

There are several known CYP systems. Five of the most important enzymes for antidepressant drug metabolism are shown in Figure 2-16. There are over 30 known CYP enzymes, and probably many more awaiting discovery and classification. Not all individuals have all the same CYP enzymes. In such cases, their enzymes are said to be polymorphic. For example, about 5–10% of Caucasians are poor metabolizers via the enzyme CYP 2D6, and approximately 20% of Asians may have reduced activity of another CYP enzyme, 2C19. Such individuals with genetically low enzyme activity must metabolize drugs by alternative routes that may not be as efficient as the traditional routes; thus, these patients often have elevated drug levels in their bloodstreams and in their brains compared to individuals with normal enzyme activity. Other individuals may inherit a CYP enzyme that is extensively active compared to normal enzyme activity, and thus have lower drug levels compared to patients with normal enzyme activity. The genes for these CYP enzymes can now be measured and can be used to predict which patients might need to have up or down dosage adjustments of certain drugs for best results.

CYP 1A2

One important CYP enzyme is 1A2. Several antipsychotics and antidepressants are substrates for 1A2, as are caffeine and theophylline (Figure 2-17). An inhibitor

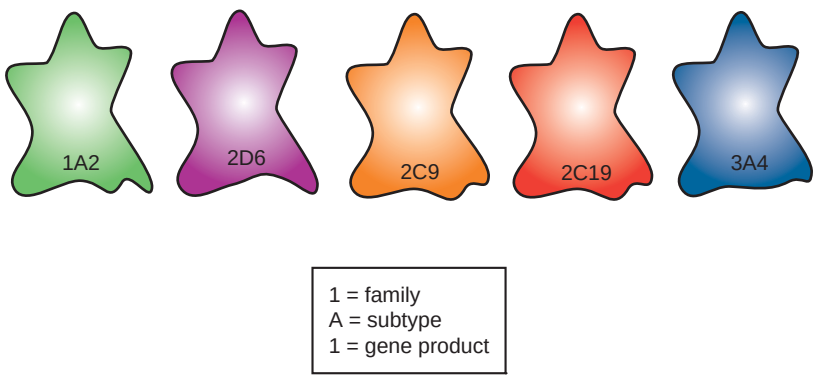


Figure 2-16. Five CYP enzymes. There are many cytochrome P450 (CYP) systems; these are classified according to family, subtype, and gene product. Five of the most important are shown here: CYP 1A2, 2D6, 2C9, 2C19, and 3A4.

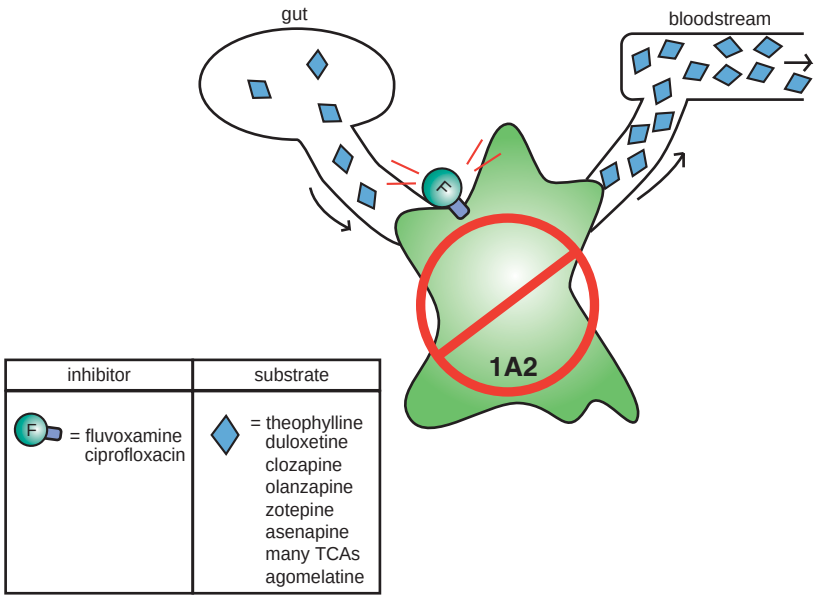


Figure 2-17. Consequences of CYP 1A2 inhibition. Numerous drugs (theophylline, duloxetine, clozapine, olanzapine, zotepine, asenapine, certain tricyclic antidepressants (TCAs), and agomelatine) are substrates for CYP 1A2. Thus, in the presence of a CYP 1A2 inhibitor (fluvoxamine, ciprofloxacin) their levels will rise. In many cases, this means that the dose of the substrate must often be lowered in order to avoid side effects.

of 1A2 is the antidepressant fluvoxamine (Figure 2-17). This means that when substrates of 1A2, such as olanzapine, clozapine, zotepine, asenapine, duloxetine, or theophylline, are given concomitantly with an inhibitor of 1A2, such as fluvoxamine, the blood and brain levels of 1A2 substrates could rise (Figure 2-17). Although this may not be particularly clinically important for olanzapine or asenapine (possibly causing slightly increased sedation), it could potentially raise plasma levels sufficiently in the case of clozapine, zotepine, duloxetine, or theophylline to increase side effects, including possibly increasing the risk of seizures. Thus, the dose of clozapine or zotepine (or olanzapine and asenapine, as well as duloxetine) may need to be lowered when administered with fluvoxamine, or an antidepressant other than fluvoxamine may need to be chosen.

1A2 can also be induced, or increased in activity, by smoking. When patients smoke, any substrate of 1A2 may have its blood and brain levels fall and require more dosage. Also, patients stabilized on an antipsychotic dose who start smoking may relapse if the drug levels fall too low. Cigarette smokers may require higher doses of 1A2 substrates than nonsmokers (Figure 2-18).

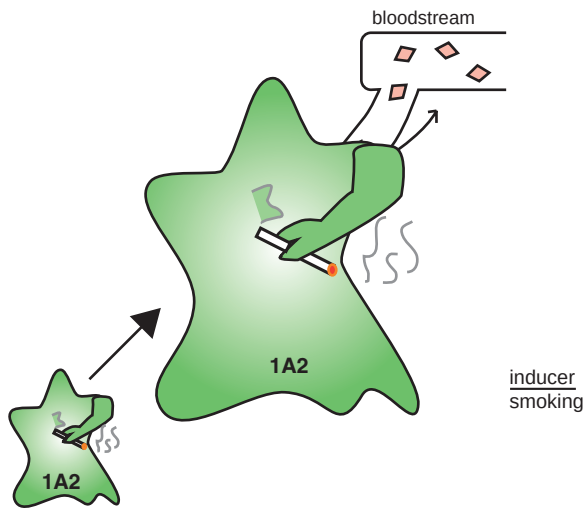
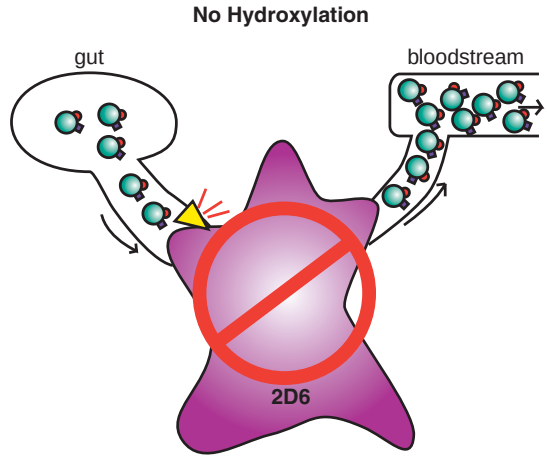


Figure 2-18. CYP 1A2 and smoking. Cigarette smoking, quite common among patients with schizophrenia, can induce the enzyme CYP 1A2 and lower the concentration of drugs metabolized by this enzyme, such as olanzapine, clozapine, zotepine, and others. Smokers may also require higher doses of these drugs than nonsmokers.

CYP 2D6

Another CYP enzyme of importance to many psychotropic drugs is 2D6. Many antipsychotics and some antidepressants are substrates for 2D6, and several antidepressants are also inhibitors of this enzyme (Figure 2-19). This enzyme converts two drugs, risperidone and venlafaxine, into active drugs (i.e., paliperidone and desvenlafaxine, respectively) rather than inactive metabolites. Giving a substrate of 2D6 to a patient who is either a genetically poor metabolizer of this enzyme or who is taking an inhibitor of



some substrates	some inhibitors
= TCA thioridazine codeine some beta blockers atomoxetine venlafaxine duloxetine paroxetine risperidone clozapine olanzapine aripiprazole iloperidone	= paroxetine fluoxetine duloxetine bupropion quinidine ritonavir asenapine

Figure 2-19. Consequences of CYP 2D6 inhibition. If a tricyclic antidepressant (a substrate for CYP 2D6) is given concomitantly with an agent that is an inhibitor of CYP 2D6 (e.g., paroxetine, fluoxetine), this will cause the levels of the tricyclic antidepressant to increase, which can be toxic. Therefore either monitoring of tricyclic plasma concentration with dose reduction or avoidance of this combination is required. Many other psychotropic medications are also substrates for CYP 2D6 and may therefore have increased blood levels when given with a CYP 2D6 inhibitor.

2D6 can raise the blood and brain levels of the substrate. This can be especially important for patients taking the 2D6 substrates tricyclic antidepressants, atomoxetine, thioridazine, iloperidone, and codeine, for example, so dose adjustments or using an alternative drug may be necessary for maximum safety and efficacy. Asenapine is an inhibitor of 2D6 and can raise the levels of drugs that are substrates of 2D6.

CYP 3A4

This enzyme metabolizes several psychotropic drugs as well as several of the HMG-CoA reductase inhibitors (statins) for treating high cholesterol (Figure 2-20). Several psychotropic drugs are weak inhibitors of this enzyme, including the antidepressants fluvoxamine, nefazodone, and the active metabolite of fluoxetine, norfluoxetine (Figure 2-20). Several nonpsychotropic drugs are powerful inhibitors of 3A4, including ketoconazole (antifungal), protease inhibitors (for AIDS/HIV), and erythromycin (antibiotic) (Figure 2-20). For the substrates of 3A4, co-administration of a 3A4 inhibitor may require dosage reduction of the substrate. Specifically, combining a 3A4 inhibitor with the 3A4 substrate pimozide can result in elevated plasma pimozide levels, with consequent QTc prolongation and dangerous cardiac arrhythmias. Combining a 3A4 inhibitor with alprazolam or triazolam can cause significant sedation due to elevated plasma drug levels of these latter agents. Combining a 3A4 inhibitor with certain cholesterol-lowering drugs that are 3A4 substrates (e.g., simvastatin, atorvastatin, lovastatin, or cerevastatin, but not pravastatin or fluvastatin) can increase the risk of muscle damage and rhabdomyolysis from elevated plasma levels of these statins.

There are also some drugs that can induce 3A4, including carbamazepine, rifampin, and some reverse transcriptase inhibitors for HIV/AIDS (Figure 2-21). Since carbamazepine is a mood stabilizer frequently mixed with atypical antipsychotics, it is possible that carbamazepine added to the regimen of a patient previously stabilized on clozapine, quetiapine, ziprasidone, sertindole, aripiprazole, iloperidone, lurasidone, or zotepine could reduce the blood and brain

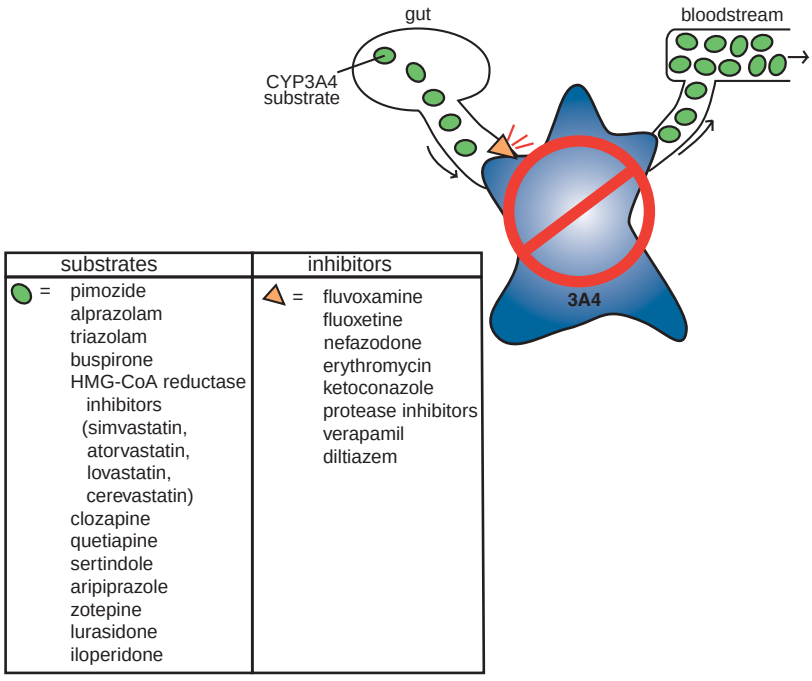


Figure 2-20. Substrates and inhibitors for CYP 3A4. The antipsychotic pimozide, the benzodiazepines alprazolam and triazolam, the anxiolytic buspirone, HMG-CoA reductase inhibitors (statins), and multiple antipsychotics are all substrates for CYP 3A4. Fluvoxamine, fluoxetine, and nefazodone are moderate CYP 3A4 inhibitors, as are some nonpsychotropic agents.

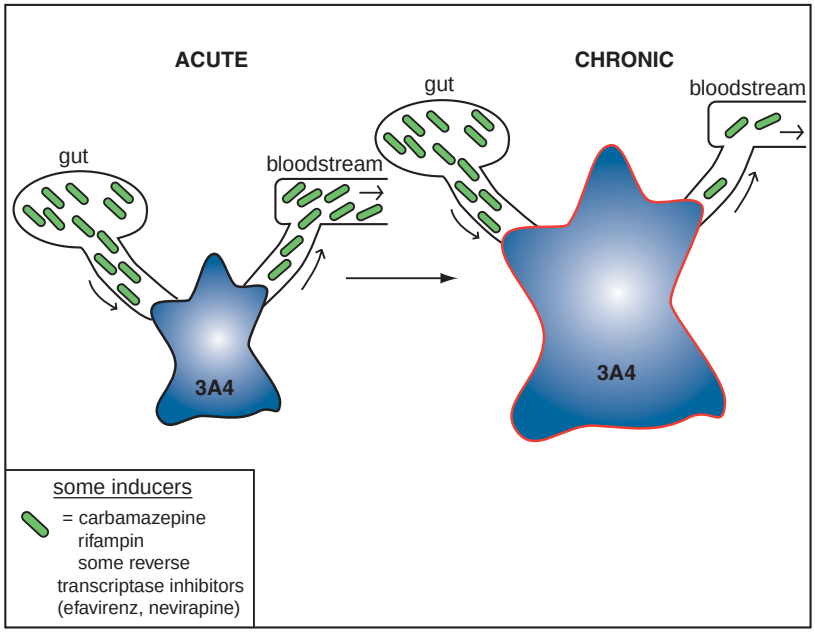


Figure 2-21. CYP 3A4 induced by carbamazepine. The enzyme CYP 3A4 can be induced by the anticonvulsant and mood stabilizer carbamazepine, as well as by rifampin and some reverse transcriptase inhibitors. This would lead to increased metabolism of substrates for 3A4 (e.g., clozapine, quetiapine, ziprasidone, sertindole, aripiprazole, and zotepine) and may therefore require higher doses of these agents when given concomitantly with carbamazepine.

levels of these agents, requiring their doses to be increased. On the other hand, if carbamazepine is stopped in a patient receiving one of these atypical antipsychotics, their doses may need to be reduced, because the autoinduction of 3A4 by carbamazepine will reverse over time.

Drug interactions mediated by CYP enzymes are constantly being discovered, and the active clinician who combines drugs must be alert to these, and thus be continually updated on what drug interactions are important. Here we present only the general concepts of drug interactions at CYP enzyme systems, but the

specifics should be found in a comprehensive and up-to-date reference source (such as *Stahl's Essential Psychopharmacology: the Prescriber's Guide*, a companion to this textbook) before prescribing.

Summary

About a third of psychotropic drugs in clinical practice bind to a neurotransmitter transporter, and another third of psychotropic drugs bind to G-protein-linked receptors. These two molecular sites of action, their impact upon neurotransmission, and various specific drugs that act at these sites have all been reviewed in this chapter.

Specifically, there are two subclasses of plasma membrane transporters for neurotransmitters and three subclasses of intracellular synaptic vesicular transporters for neurotransmitters. The monoamine transporters (SERT for serotonin, NET for norepinephrine, and DAT for dopamine) are key targets for most of the known antidepressants. In addition, stimulants target DAT. The vesicular transporter for all three of these monoamines is known as VMAT2 (vesicular monoamine transporter 2) and is also a target of the stimulant amphetamine.

G-protein receptors are the most common targets of psychotropic drugs, and their actions can lead to both therapeutic and side effects. Drug actions at these receptors occur in a spectrum, from full agonist actions, to partial agonist actions, to antagonism, and even to inverse agonism. Natural neurotransmitters are full agonists, as are some drugs used in clinical practice. However, most drugs that act directly on G-protein-linked receptors act as antagonists. A few act as partial agonists, and some as inverse agonists. Each drug interacting at a G-protein-linked receptor causes a conformational change in that receptor that defines where on the agonist spectrum it will act. Thus, a full agonist produces a conformational change that turns on signal transduction and second-messenger formation to the maximum extent. One novel concept is that of a partial agonist, which acts somewhat like an agonist, but to a lesser extent. An antagonist causes a conformational change that stabilizes the receptor in the baseline state and thus is "silent." In the presence of agonists or partial agonists, an antagonist causes the receptor to return to this baseline state as well, and thus reverses their actions. A novel receptor action is that of an inverse agonist that leads to a conformation of the receptor that stops all activity, even baseline actions. Understanding the agonist spectrum can lead to prediction of downstream consequences on signal transduction, including clinical actions.

Chapter 3

Ion channels as targets of psychopharmacological drug action

Many important psychopharmacological drugs target ion channels. The roles of ion channels as important regulators of synaptic neurotransmission were covered in Chapter 1. Here we discuss how targeting these molecular sites causes alterations in synaptic neurotransmission that are linked in turn to the therapeutic actions of various psychotropic drugs. Specifically, we cover ligand-gated ion channels and voltage-sensitive ion channels as targets of psychopharmacological drug action.

Ligand-gated ion channels as targets of psychopharmacological drug action

Ligand-gated ion channels, ionotropic receptors, and ion-channel-linked receptors: different terms for the same receptor/ion-channel complex

Ions normally cannot penetrate membranes because of their charge. In order to selectively control access of ions into and out of neurons, their membranes are decorated with all sorts of ion channels. The most important ion channels in psychopharmacology regulate calcium, sodium, chloride, and potassium. Many can be modified by various drugs, and this will be discussed throughout this chapter.

There are two major classes of ion channels, and each class has several names. One class of ion channels is opened by neurotransmitters and goes by the names *ligand-gated ion channels*, *ionotropic receptors*, and *ion-channel-linked receptors*. These channels and their associated receptors will be discussed next. The other major class of ion channel is opened by the charge or voltage across the membrane and is called either a *voltage-sensitive* or a *voltage-gated* ion channel; these will be discussed later in this chapter.

Ion channels that are opened and closed by actions of neurotransmitter ligands at receptors acting as gatekeepers are shown conceptually in Figure 3-1. When a neurotransmitter binds to a gatekeeper receptor on an ion channel, that neurotransmitter causes a conformational change in the receptor that opens the ion channel (Figure 3-1A). A neurotransmitter, drug, or hormone that binds to a receptor is sometimes called a *ligand* (literally, "tying"). Thus, ion channels linked to receptors that regulate their opening and closing are often called *ligand-gated ion channels*. Since these ion channels are also receptors, they are sometimes also called *ionotropic receptors* or *ion-channel-linked receptors*.

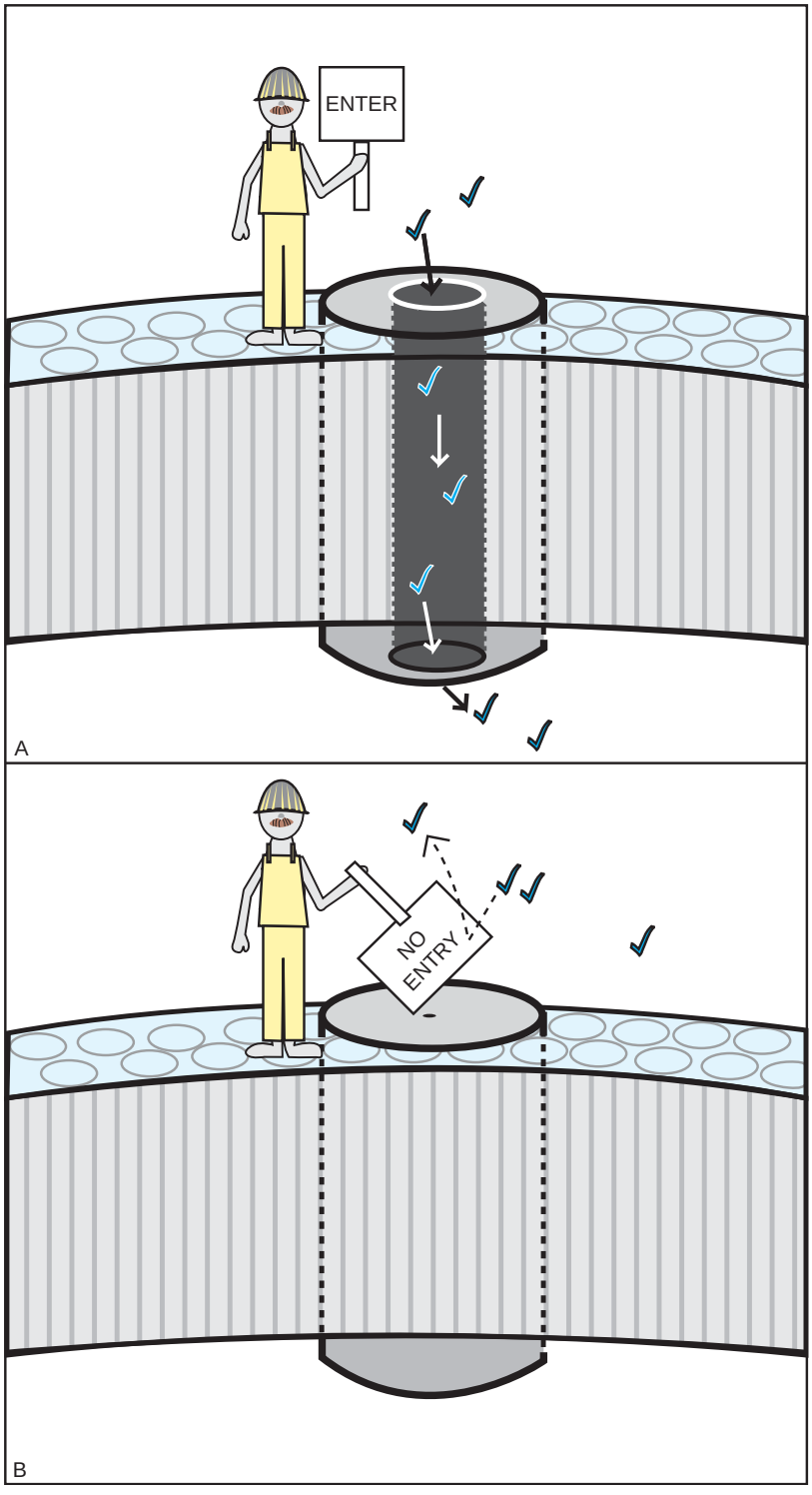


Figure 3-1. Ligand-gated ion channel gatekeeper. This schematic shows a ligand-gated ion channel. In panel A, a receptor is serving as a molecular gatekeeper that acts on instruction from neurotransmission to open the channel and allow ions to travel into the cell. In panel B, the gatekeeper is keeping the channel closed so that ions cannot get into the cell. Ligand-gated ion channels are a type of receptor that forms an ion channel and are thus also called ion-channel-linked receptors or ionotropic receptors.

These terms will be used interchangeably with ligand-gated ion channels here.

Numerous drugs act at many sites around such receptor/ion-channel complexes, leading to a wide variety of modifications of receptor/ion-channel actions. These modifications not only immediately alter the flow of ions through the channels, but with a delay can also change the downstream events that result from transduction of the signal that begins at these receptors. The downstream actions have been extensively discussed in Chapter 1 and include both activation and inactivation of phosphoproteins, shifting the activity of enzymes, the sensitivity of receptors, and the conductivity of ion channels. Other downstream actions include changes in gene expression and thus changes in which proteins are synthesized and which functions are amplified. Such functions can range from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the ionotropic receptor, and many more. The reader should have a good command of the function of signal transduction pathways described in Chapter 1 in order to understand how drugs acting at ligand-gated ion channels modify the signal transduction that arises from these receptors.

Drug-induced modifications in signal transduction from ionotropic (sometimes called ionotrophic) receptors can have profound actions on psychiatric symptoms. About a fifth of psychotropic drugs currently utilized in clinical practice, including many drugs for the treatment of anxiety and insomnia such as the benzodiazepines, are known to act at these receptors. Because ionotropic receptors immediately change the flow of ions, drugs that act on these receptors can have an almost immediate effect, which is why many anxiolytics and hypnotics that act at these receptors may have immediate clinical onset. This is in contrast to the actions of many drugs at G-protein-linked receptors described in Chapter 2, some of which have clinical effects – such as antidepressant actions – that may occur with a delay necessitated by awaiting initiation of changes in cellular functions activated through the signal transduction cascade. Here we will describe how various drugs stimulate or block various molecular sites around the receptor/ion-channel complex. Throughout the textbook we will show how specific drugs acting at specific ionotropic receptors have specific actions on specific psychiatric disorders.

Ligand-gated ion channels: structure and function

Are ligand-gated ion channels receptors or ion channels? The answer is "yes" – ligand-gated ion channels are a type of receptor and they also form an ion channel. That is why they are called not only a channel (ligand-gated ion channel) but also a receptor (ionotropic receptor or ion-channel-linked receptor). These terms try to capture the dual function of these ion channels/receptors.

Ligand-gated ion channels comprise several long strings of amino acids assembled as subunits around an ion channel. Decorating these subunits are also multiple binding sites for everything from neurotransmitters to ions to drugs. That is, these complex proteins have several sites where some ions travel through a channel and others also bind to the channel; where one neurotransmitter or even two cotransmitters act at separate and distinct binding sites; where numerous allosteric modulators – i.e., natural substances or drugs that bind to a site different than where the neurotransmitter binds – increase or decrease the sensitivity of channel opening.

Pentameric subtypes

Many ligand-gated ion channels are assembled from five protein subunits; that is why they are called pentameric. The subunits for pentameric subtypes of ligand-gated ion channels each have four transmembrane regions (Figure 3-2A). These membrane proteins go in and out of the membrane four times (Figure 3-2A). When five copies of these subunits are selected (Figure 3-2B), they come together in space to form a fully functional pentameric receptor with the ion channel in the middle (Figure 3-2C). The receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel. This pentameric structure is typical for $GABA_A$ receptors, nicotinic cholinergic receptors, serotonin $5HT_3$ receptors, and glycine receptors (Table 3-1). Drugs that act directly on pentameric ligand-gated ion channels are listed in Table 3-2.

If this structure were not complicated enough, pentameric ionotropic receptors actually have many different subtypes. Subtypes of pentameric ionotropic receptors are defined based upon which forms of each

Table 3-1 Pentameric ligand-gated ion channels

4 transmembrane regions 5 subunits	
Neurotransmitter	**Receptor subtype**
Acetylcholine	Nicotinic receptors (e.g., α_7-nicotinic receptors; $\alpha_4\beta_2$-nicotinic receptors)
GABA	$GABA_A$ receptors (e.g., α_1 subunits)
Glycine	Strychnine-sensitive glycine receptors
Serotonin	$5HT_3$ receptors

of the five subunits are chosen for assembly into a fully constituted receptor. That is, there are several subtypes for each of the four transmembrane subunits, making it possible to piece together several different constellations of fully constituted receptors. Although the natural neurotransmitter binds to every subtype of ionotropic receptor, some drugs used in clinical practice, and many more in clinical trials, are able to bind selectively to one or more of these subtypes, but not to others. This may have functional and clinical consequences. Specific receptor subtypes and the specific drugs that bind to them selectively are discussed in chapters that cover their specific clinical use.

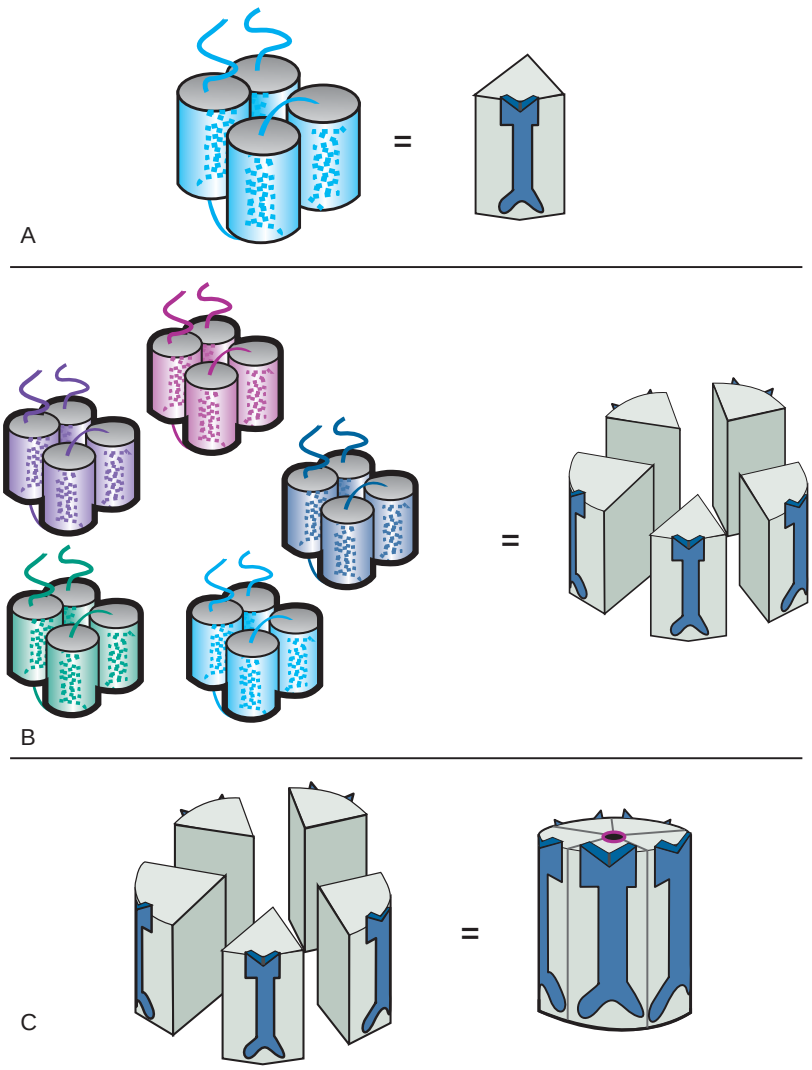


Figure 3-2. Ligand-gated ion channel structure. The four transmembrane regions of a single subunit of a pentameric ligand-gated ion channel form a cluster, as shown in panel A. An icon for this subunit is shown on the right in panel A. Five copies of the subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Pentameric ligand-gated ion channels have receptor binding sites located on all five subunits, both inside and outside the channel.

Table 3-2 Key ligand-gated ion channels directly targeted by psychotropic drugs

Neurotransmitter	Ligand-gated ion-channel receptor subtype directly targeted	Pharmacologic action	Drug class	Therapeutic action
Acetylcholine	$\alpha_4\beta_2$ nicotinic receptors	Partial agonist	Nicotinic receptor partial agonist (NRPA) (varenicline)	Smoking cessation
GABA	$GABA_A$ benzodiazepine receptors	Full agonist	Benzodiazepines	Anxiolytic
	$GABA_A$ non-benzodiazepine PAM sites	Full agonist	"Z drugs"/hypnotics (zolpidem, zaleplon, zopiclone, eszopiclone)	Improve insomnia
Glutamate	NMDA NAM channel sites/ Mg^{++} sites	Antagonist	NMDA glutamate antagonist (memantine)	Slowing progression in Alzheimer's disease
	NMDA open channel sites	Antagonist	PCP (phencyclidine) Ketamine	Hallucinogen anesthetic
Serotonin	$5HT_3$	Antagonist	Antidepressant (mirtazapine)	Unknown; reduce nausea
	$5HT_3$	Antagonist	Antiemetic	Reduce chemotherapy-induced emesis

PAM, positive allosteric modulator; NAM, negative allosteric modulator; NMDA, *N*-methyl-D-aspartate; Mg, magnesium.

Tetrameric subtypes

Ionotropic glutamate receptors have a different structure from the pentameric ionotropic receptors just discussed. The ligand-gated ion channels for glutamate comprise subunits that have three full transmembrane regions and a fourth re-entrant loop (Figure 3-3A), rather than four full transmembrane regions as shown in Figure 3-2A. When four copies of these subunits are selected (Figure 3-3B), they come together in space to form a fully functional ion channel in the middle with the four re-entrant loops lining the ion channel (Figure 3-3C). Thus, tetrameric subtypes of ion channels (Figure 3-3) are analogous to pentameric subtypes of ion channels (Figure 3-2), but have just four subunits rather than five. Receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel.

This tetrameric structure is typical of the ionotropic glutamate receptors known as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) and NMDA (*N*-methyl-D-aspartate) subtypes (Table 3-3). Drugs that act directly at tetrameric ionotropic glutamate receptors are listed in Table 3-2. Receptor subtypes for glutamate according to the selective agonist acting at that receptor, as well as the specific molecular subunits that comprise that subtype, are listed in Table 3-3. Subtype-selective drugs for ionotropic glutamate receptors are under investigation but not currently used in clinical practice.

The agonist spectrum

The concept of an agonist spectrum for G-protein-linked receptors, discussed extensively in Chapter 2, can also be applied to ligand-gated ion channels (Figure 3-4). Thus, **full agonists** change the conformation of the receptor to open the ion channel the maximal amount and frequency allowed by that binding site (Figure 3-5). This then triggers the maximal amount of downstream signal transduction possible to be mediated by this binding site. The ion channel can open to an even greater extent (i.e., more frequently) than with a full agonist alone, but this requires the help of a second receptor site, that of a positive allosteric modulator, or PAM, as will be shown later.

Table 3-3 Tetrameric ligand-gated ion channels

3 transmembrane regions and one re-entrant loop 4 subunits	
Neurotransmitter	**Receptor subtype**
Glutamate	AMPA (e.g., GluR1–4 subunits)
	KAINATE (e.g., GluR5–7, KA1–2 subunits)
	NMDA (e.g., NMDAR1, NMDAR2A–D, NMDAR3A subunits)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, *N*-methyl-D-aspartate.

Antagonists stabilize the receptor in the resting state, which is the same as the state of the receptor in the absence of agonist (Figure 3-6). Since there is no difference between the presence and absence of the antagonist, the antagonist is said to be neutral or silent. The resting state is not a fully closed ion channel, so there is some degree of ion flow through the channel even in the absence of agonist (Figure 3-6A) and even in the presence of antagonist (Figure 3-6B). This is due to occasional and infrequent opening of the channel even when an agonist is not present and even when an antagonist is present. This is called constitutive activity and is also discussed in Chapter 2 for G-protein-linked receptors. Antagonists

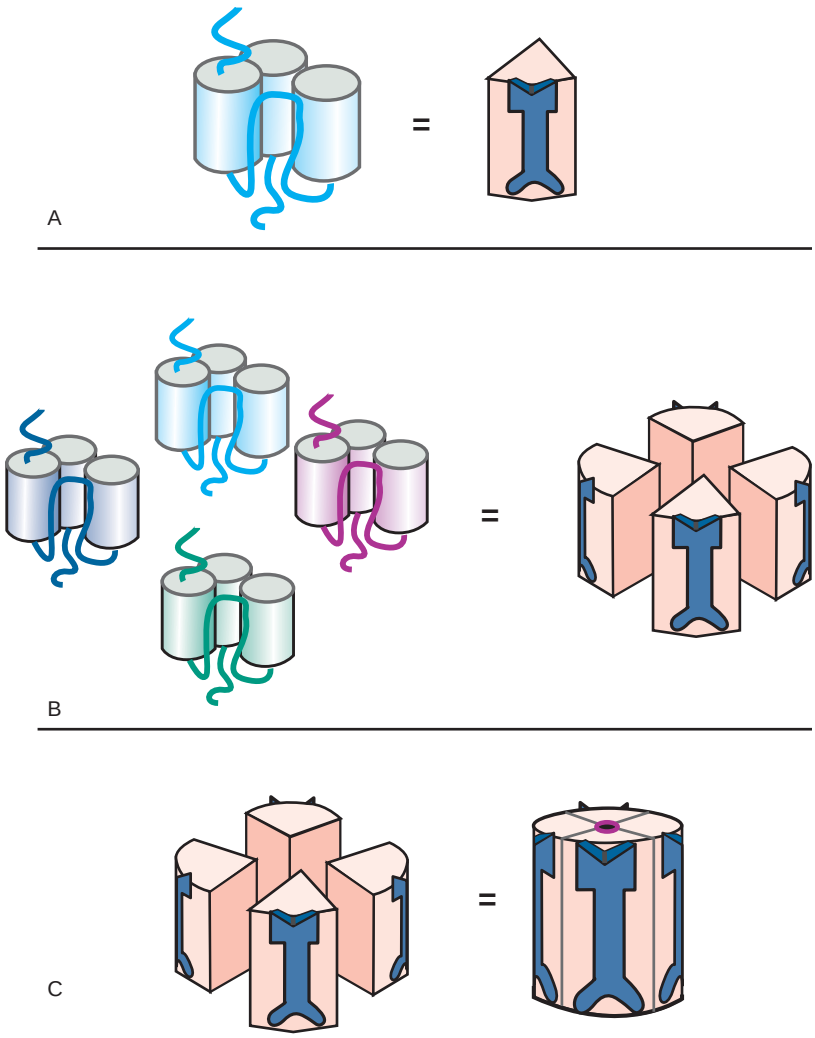


Figure 3-3. Tetrameric ligand-gated ion channel structure. A single subunit of a tetrameric ligand-gated ion channel is shown to form a cluster in panel A, with an icon for this subunit shown on the right in panel A. Four copies of these subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Tetrameric ligand-gated ion channels have receptor binding sites located on all four subunits, both inside and outside the channel.

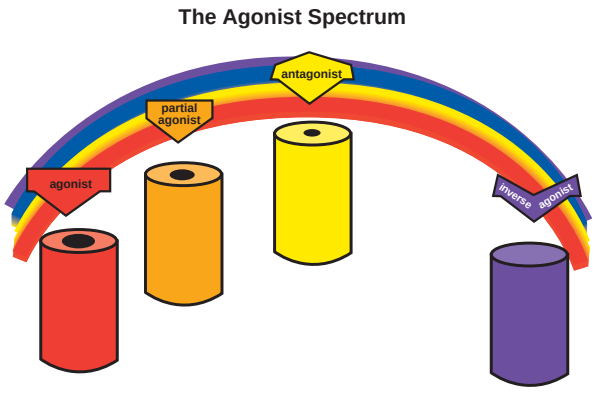


Figure 3-4. Agonist spectrum. The agonist spectrum and its corresponding effects on the ion channel are shown here. This spectrum ranges from agonists (on the far left), which open the channel the maximal amount and frequency allowed by that binding site, through antagonists (middle of the spectrum), which retain the resting state with infrequent opening of the channel, to inverse agonists (on the far right), which put the ion channel into a closed and inactive state. Between agonists and antagonists are partial agonists, which increase the degree and frequency of ion-channel opening as compared to the resting state, but not as much as a full agonist. Antagonists can block anything in the agonist spectrum, returning the ion channel to the resting state in each instance.

of ion-channel-linked receptors reverse the action of agonists (Figure 3-7) and bring the receptor conformation back to the resting baseline state, but do not block any constitutive activity.

Partial agonists produce a change in receptor conformation such that the ion channel opens to a greater extent and more frequently than in its resting state but less than in the presence of a full agonist (Figures 3-8 and 3-9). An antagonist reverses a partial agonist, just as it reverses a full agonist, returning the receptor to its resting state (Figure 3-10). Partial agonists thus produce ion flow and downstream signal transduction that is something more than the resting state in the absence of agonist, yet something less than a full agonist. Just as is the case for G-protein-linked receptors, how close this partial agonist is to a full agonist or to a silent antagonist on the agonist spectrum will determine the impact of a partial agonist on downstream signal transduction events.

The ideal therapeutic agent in some cases may need to have ion flow and signal transduction that is not too hot, yet not too cold, but just right, called the "Goldilocks" solution in Chapter 2, a concept that can apply here to ligand-gated ion channels as well. Such

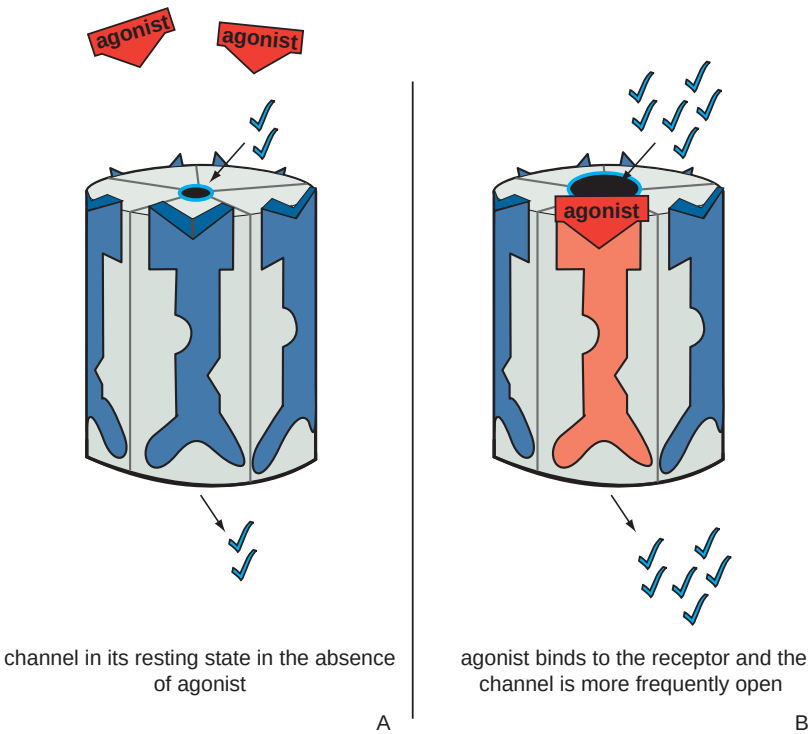


Figure 3-5. Actions of an agonist. In panel A, the ion channel is in its resting state, during which the channel opens infrequently (constitutive activity). In panel B, the agonist occupies its binding site on the ligand-gated ion channel, increasing the frequency at which the channel opens. This is represented as the red agonist turning the receptor red and opening the ion channel.

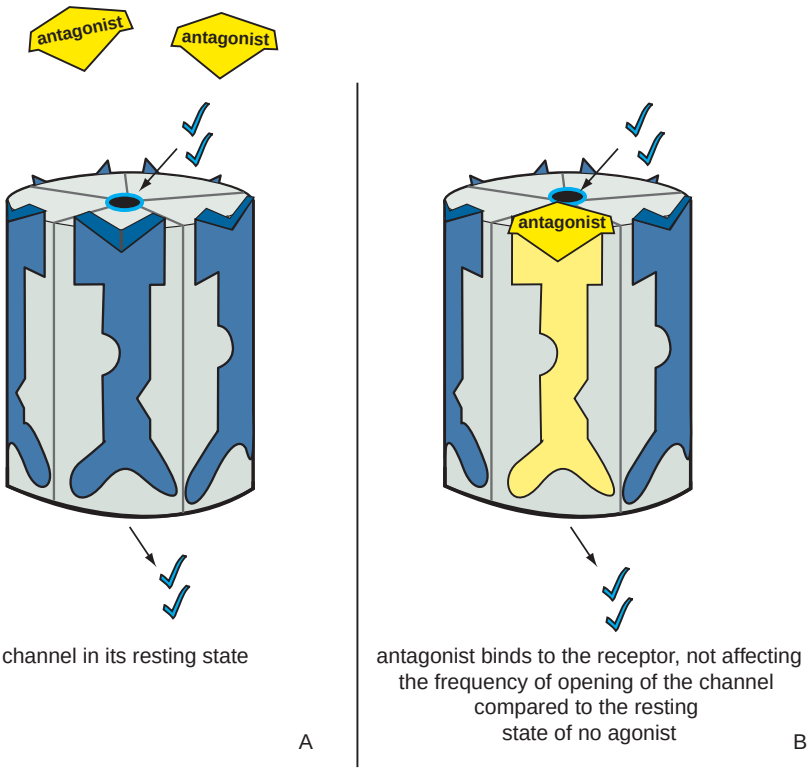


Figure 3-6. Antagonists acting alone. In panel A, the ion channel is in its resting state, during which the channel opens infrequently. In panel B, the antagonist occupies the binding site normally occupied by the agonist on the ligand-gated ion channel. However, there is no consequence to this, and the ion channel does not affect the degree or frequency of opening of the channel compared to the resting state. This is represented as the yellow antagonist docking into the binding site and turning the receptor yellow but not affecting the state of the ion channel.

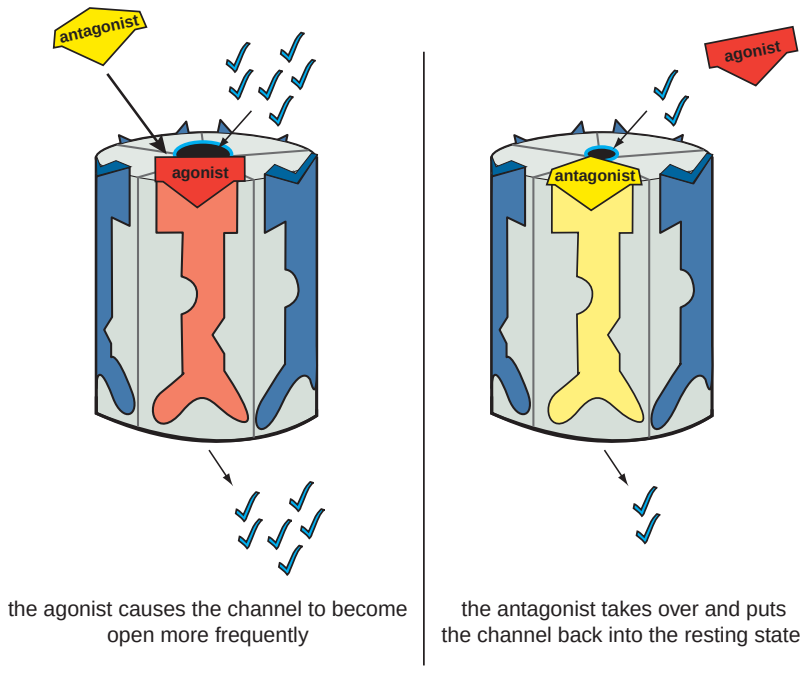


Figure 3-7. Antagonist acting in presence of agonist. In panel A, the ion channel is bound by an agonist, which causes it to open at a greater frequency than in the resting state. This is represented as the red agonist turning the receptor red and opening the ion channel as it docks into its binding site. In panel B, the yellow antagonist prevails and shoves the red agonist off the binding site, reversing the agonist's actions and restoring the resting state. Thus, the ion channel has returned to its status before the agonist acted.

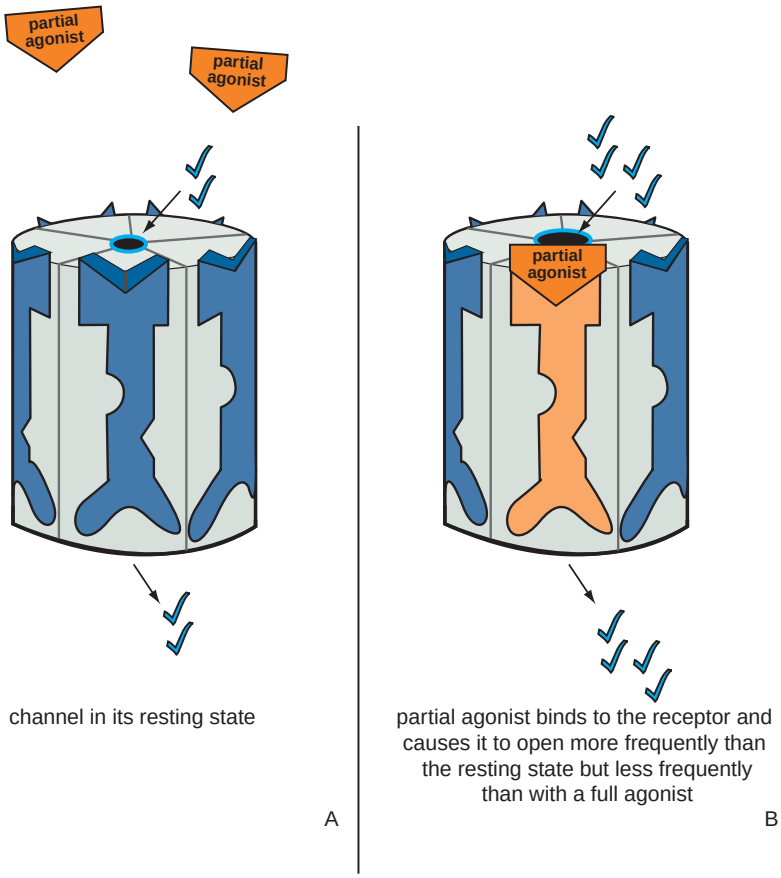


Figure 3-8. Actions of a partial agonist. In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the partial agonist occupies its binding site on the ligand-gated ion channel and produces a conformational change such that the ion channel opens to a greater extent and at a greater frequency than in the resting state, though less than in the presence of a full agonist. This is depicted by the orange partial agonist turning the receptor orange and partially but not fully opening the ion channel.

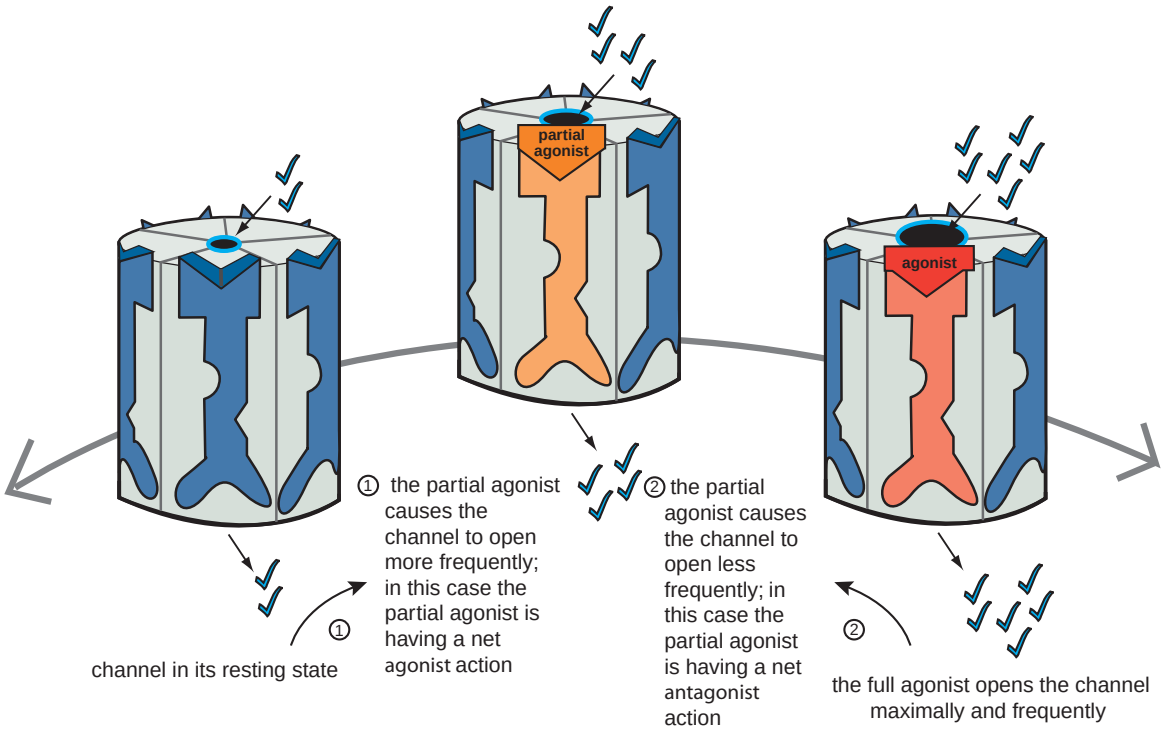


Figure 3-9. Net effect of partial agonist. Partial agonists act either as net agonists or as net antagonists, depending on the amount of agonist present. When full agonist is absent (on the far left), a partial agonist causes the channel to open more frequently as compared to the resting state and thus has a net agonist action (moving from left to right). However, in the presence of a full agonist (on the far right), a partial agonist decreases the frequency of channel opening in comparison to the full agonist and thus acts as a net antagonist (moving from right to left).

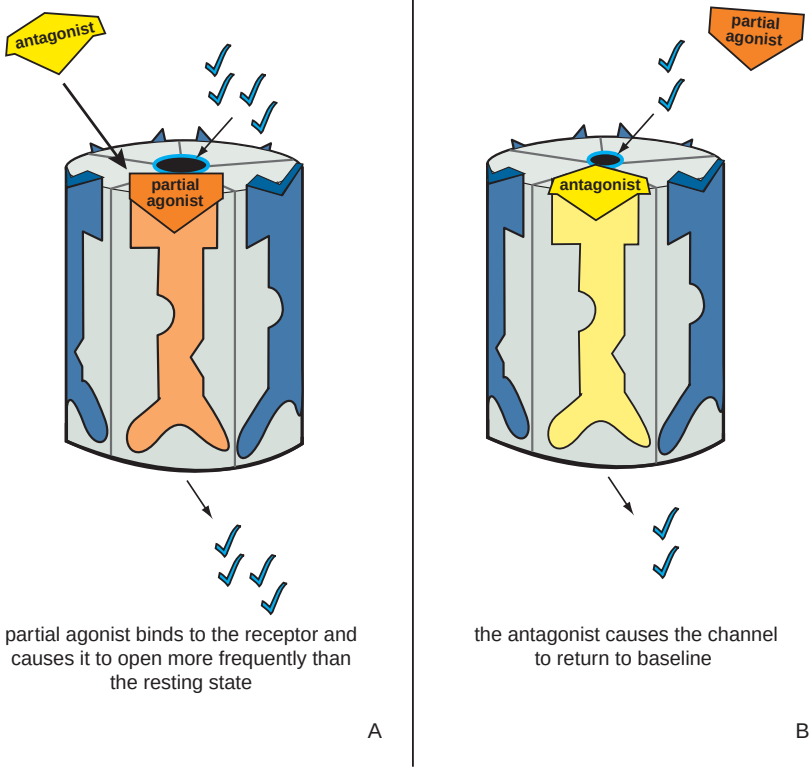


Figure 3-10. Antagonist acting in presence of partial agonist. In panel A, a partial agonist occupies its binding site and causes the ion channel to open more frequently than in the resting state. This is represented as the orange partial agonist docking to its binding site, turning the receptor orange, and partially opening the ion channel. In panel B, the yellow antagonist prevails and shoves the orange partial agonist off the binding site, reversing the partial agonist's actions. Thus the ion channel is returned to its resting state.

an ideal state may vary from one clinical situation to another, depending upon the balance between full agonism and silent antagonism that is desired. In cases where there is unstable neurotransmission throughout the brain, finding such a balance may stabilize receptor output somewhere between too much and too little downstream action. For this reason, partial agonists are also called "*stabilizers*," since they have the theoretical capacity to find the stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 3-9).

Just as is the case for G-protein-linked receptors, partial agonists at ligand-gated ion channels can appear as net agonists, or as net antagonists, depending upon the amount of naturally occurring full agonist neurotransmitter that is present. Thus, when a full agonist neurotransmitter is absent, a partial agonist will be a net agonist (Figure 3-9). That is, from the resting state, a partial agonist initiates somewhat of an increase in the ion flow and downstream signal transduction cascade from the ion-channel-linked receptor. However, when full agonist neurotransmitter is present, the same partial agonist will become a net antagonist (Figure 3-9): it will decrease the level of full signal output to a lesser level, but not to zero. Thus, a partial agonist can simultaneously *boost* deficient neurotransmitter activity yet *block* excessive neurotransmitter activity, another reason that partial agonists are called stabilizers. An agonist and an antagonist in the same molecule acting at ligand-gated ion channels is quite an interesting new dimension to therapeutics. This concept has led to proposals that partial agonists could treat not only states that are theoretically deficient in full agonist, but also states that are theoretically in excess of full agonist. As mentioned in the discussion of G-protein-linked receptors in Chapter 2, a partial agonist at ligand-gated ion channels could also theoretically treat states that are mixtures of both excessive and deficient neurotransmitter activity. Partial agonists at ligand-gated ion channels are just beginning to enter use in clinical practice (Table 3-2), and several more are in clinical development.

Inverse agonists at ligand-gated ion channels are different from simple antagonists, and are neither neutral nor silent. Inverse agonists are explained in Chapter 2 in relation to G-protein-linked receptors. Inverse agonists at ligand-gated ion channels are thought to produce

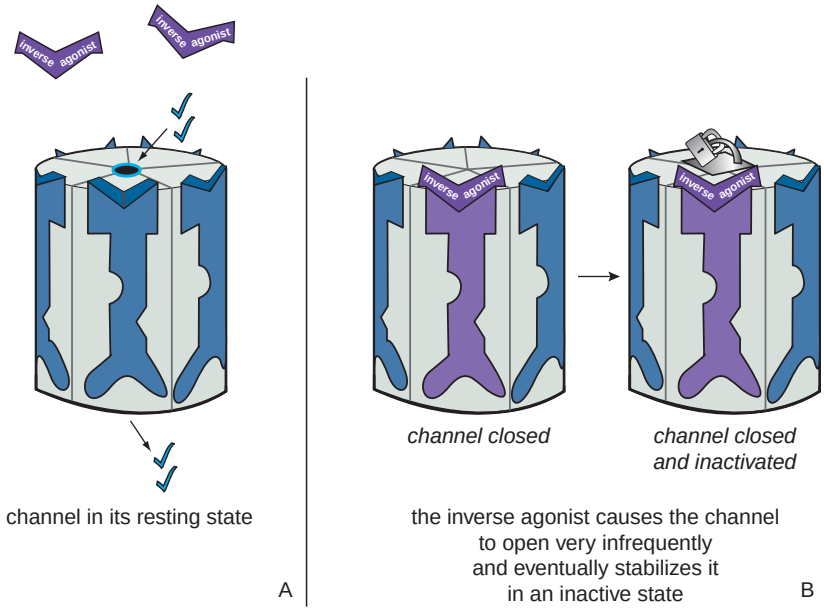


Figure 3-11. Actions of an inverse agonist. In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the inverse agonist occupies the binding site on the ligand-gated ion channel and causes it to close. This is the opposite of what an agonist does and is represented by the purple inverse agonist turning the receptor purple and closing the ion channel. Eventually, the inverse agonist stabilizes the ion channel in an inactive state, represented by the padlock on the channel itself.

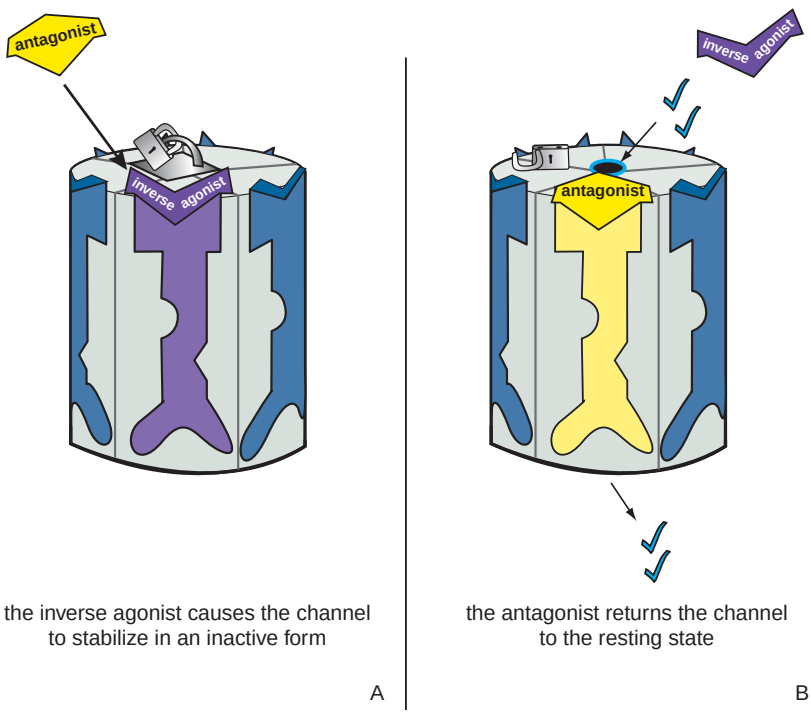


Figure 3-12. Antagonist acting in presence of inverse agonist. In panel A, the ion channel has been stabilized in an inactive form by the inverse agonist occupying its binding site on the ligand-gated ion channel. This is represented as the purple inverse agonist turning the receptor purple and closing and padlocking the ion channel. In panel B, the yellow antagonist prevails and shoves the purple inverse agonist off the binding site, returning the ion channel to its resting state. In this way, the antagonist's effects on an inverse agonist's actions are similar to its effects on an agonist's actions; namely, it returns the ion channel to its resting state. However, in the presence of an inverse agonist, the antagonist increases the frequency of channel opening, whereas in the presence of an agonist, the antagonist decreases the frequency of channel opening. Thus an antagonist can reverse the actions of either an agonist or an inverse agonist despite the fact that it does nothing on its own.

a conformational change in these receptors that first closes the channel and then stabilizes it in an inactive form (Figure 3-11). Thus, this inactive conformation (Figure 3-11B) produces a functional reduction in ion flow and in consequent signal transduction compared to the resting state (Figure 3-11A) that is even less than that produced when there is either no agonist present or when a silent antagonist is present. Antagonists reverse

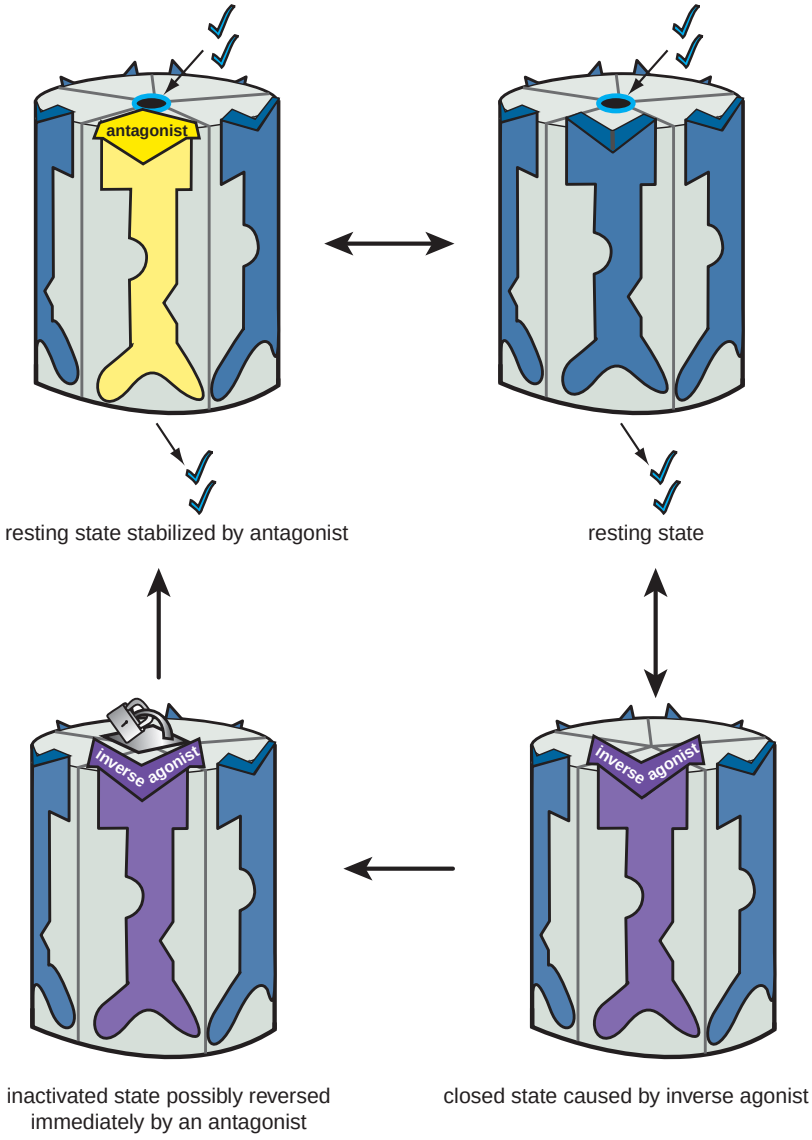


Figure 3-13. Inverse agonist actions reversed by antagonist. Antagonists cause conformational change in ligand-gated ion channels that stabilizes the receptors in the resting state (top left), the same state they are in when no agonist or inverse agonist is present (top right). Inverse agonists cause conformational change that closes the ion channel (bottom right). When an inverse agonist is bound over time, it may eventually stabilize the ion channel in an inactive conformation (bottom left). This stabilized conformation of an inactive ion channel can be quickly reversed by an antagonist, which restabilizes it in the resting state (top left).

this inactive state caused by inverse agonists, returning the channel to the resting state (Figure 3-12).

In many ways, therefore, an inverse agonist does the *opposite* of an agonist. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. Also, in contrast to antagonists, which stabilize the resting state, inverse agonists stabilize an inactivated state (Figures 3-11 and 3-13). It is not yet clear if the inactivated state of the inverse agonist can be distinguished clinically from the resting state of the silent antagonist at ionotropic receptors. In the meantime, inverse agonists remain an interesting pharmacological concept.

In summary, ion-channel-linked receptors act along an agonist spectrum, and drugs have been described that can produce conformational changes in these receptors to create any state from full agonist, to partial agonist, to silent antagonist, to inverse agonist (Figure 3-4). When one considers signal transduction along this spectrum, it is easy to understand why agents at each point along the agonist spectrum differ so much from each other, and why their clinical actions are so different.

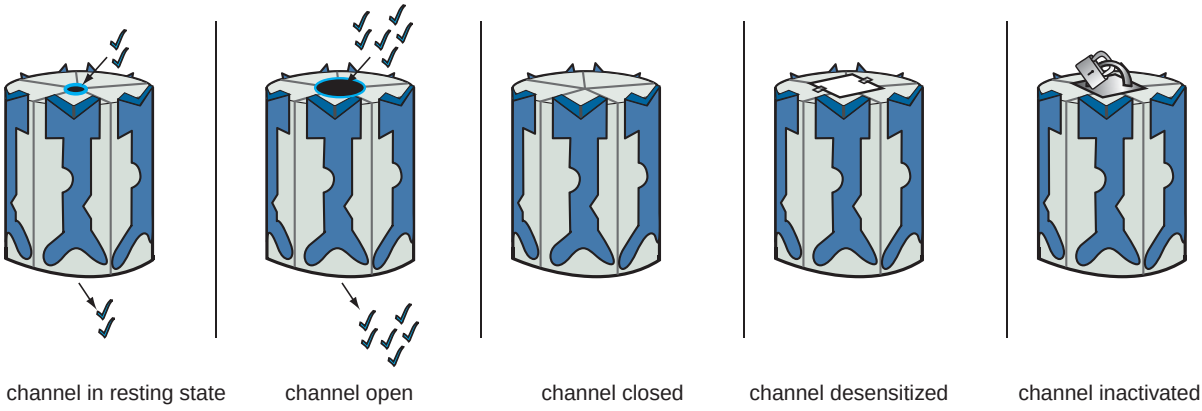


Figure 3-14. Five states of ligand-gated ion channels. Summarized here are five well-known states of ligand-gated ion channels. In the resting state, ligand-gated ion channels open infrequently, with consequent constitutive activity that may or may not lead to detectable signal transduction. In the open state, ligand-gated ion channels open to allow ion conductance through the channel, leading to signal transduction. In the closed state, ligand-gated ion channels are closed, allowing no ion flow to occur and thus reducing signal transduction to even less than is produced in the resting state. Channel desensitization is an adaptive state in which the receptor stops responding to agonist even if it is still bound. Channel inactivation is a state in which a closed ion channel over time becomes stabilized in an inactive conformation.

Different states of ligand-gated ion channels

There are even more states of ligand-gated ion channels than those determined by the agonist spectrum discussed above and shown in Figures 3-4 through 3-13. The states discussed so far are those that occur predominantly with acute administration of agents that work across the agonist spectrum. These range from the maximal opening of the ion channel caused by a full agonist to the maximal closing of the ion channel caused by an inverse agonist. Such changes in conformation caused by the acute action of agents across this spectrum are subject to change over time, because these receptors have the capacity to adapt, particularly when there is chronic or excessive exposure to such agents.

We have already discussed the resting state, the open state, and the closed state shown in Figure 3-14. The best-known adaptive states are those of desensitization and inactivation, also shown in Figure 3-14. We have also briefly discussed inactivation as a state that can be caused by acute administration of an inverse agonist, beginning with a rapid conformational change in the ion channel that first closes it, but over time stabilizes the channel in an inactive conformation that can be relatively quickly reversed by an antagonist, which then restabilizes the ion channel in the resting state (Figures 3-11 through 3-13).

Desensitization is yet another state of the ligand-gated ion channel shown in Figure 3-14. Ion-channel-linked receptor desensitization can be caused by prolonged exposure to agonists, and may be a way for receptors to protect themselves from overstimulation. An agonist acting at a ligand-gated ion channel first induces a change in receptor conformation that opens the channel, but the continuous presence of the agonist over time leads to another conformational change where the receptor essentially stops responding to the agonist even though the agonist is still present. This receptor is then considered to be desensitized (Figures 3-14 and 3-15). This state of desensitization can at first be reversed relatively quickly by removal of the agonist (Figure 3-15). However, if the agonist stays much longer, on the order of hours, then the receptor converts from a state of simple desensitization to one of inactivation (Figure 3-15). This state does not reverse simply upon removal of the agonist, since it also takes hours in the absence of agonist to revert to the resting state where the receptor is again sensitive to new exposure to agonist (Figure 3-15).

The state of inactivation may be best characterized for nicotinic cholinergic receptors, ligand-gated ion channels that are normally responsive to the endogenous neurotransmitter acetylcholine. Acetylcholine is quickly hydrolyzed by an abundance of the enzyme acetylcholinesterase, so it rarely gets the chance to desensitize and inactivate its nicotinic receptors. However, the drug nicotine is not hydrolyzed by acetylcholinesterase, and is famous for stimulating nicotinic cholinergic receptors so profoundly and so

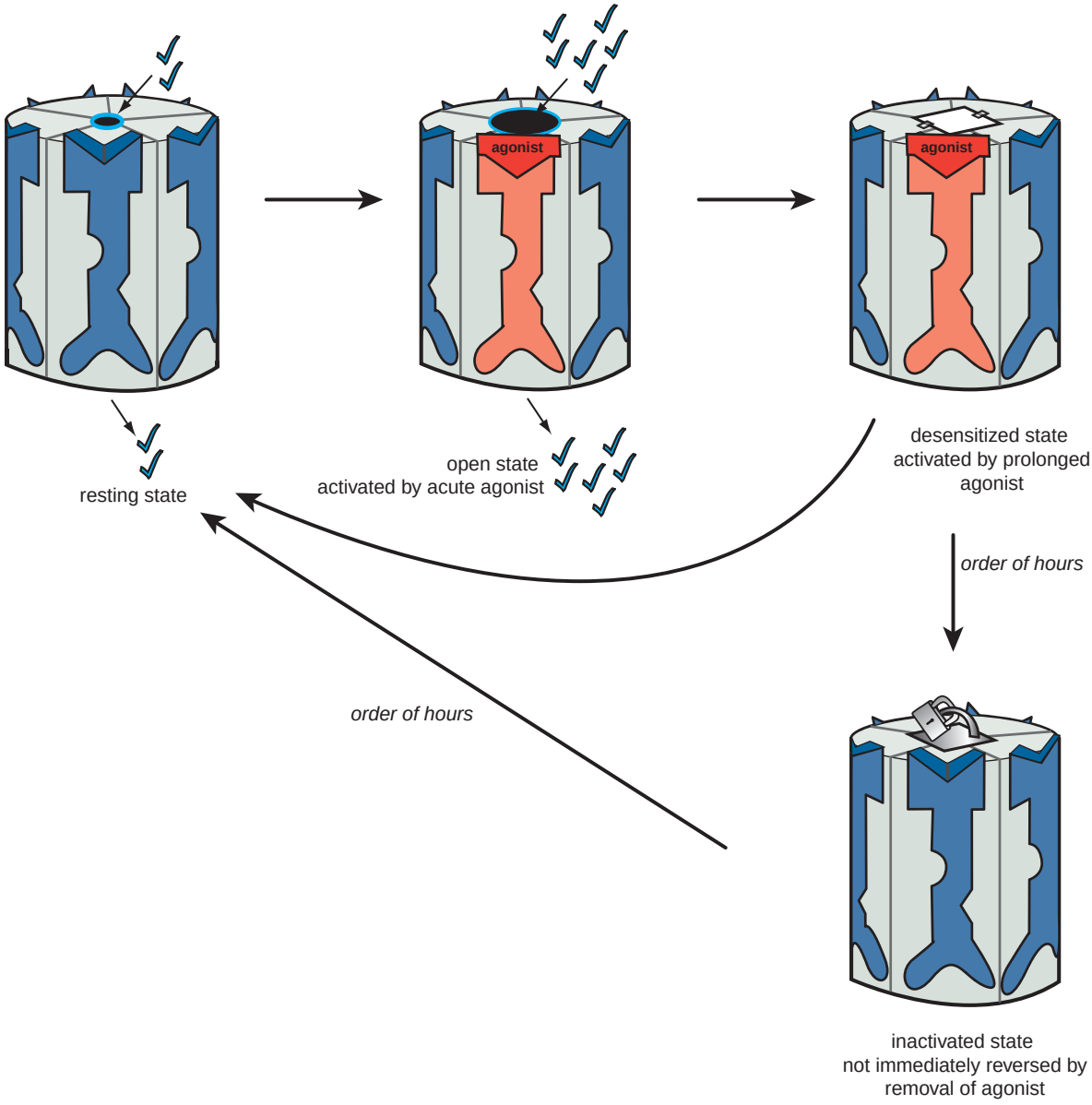
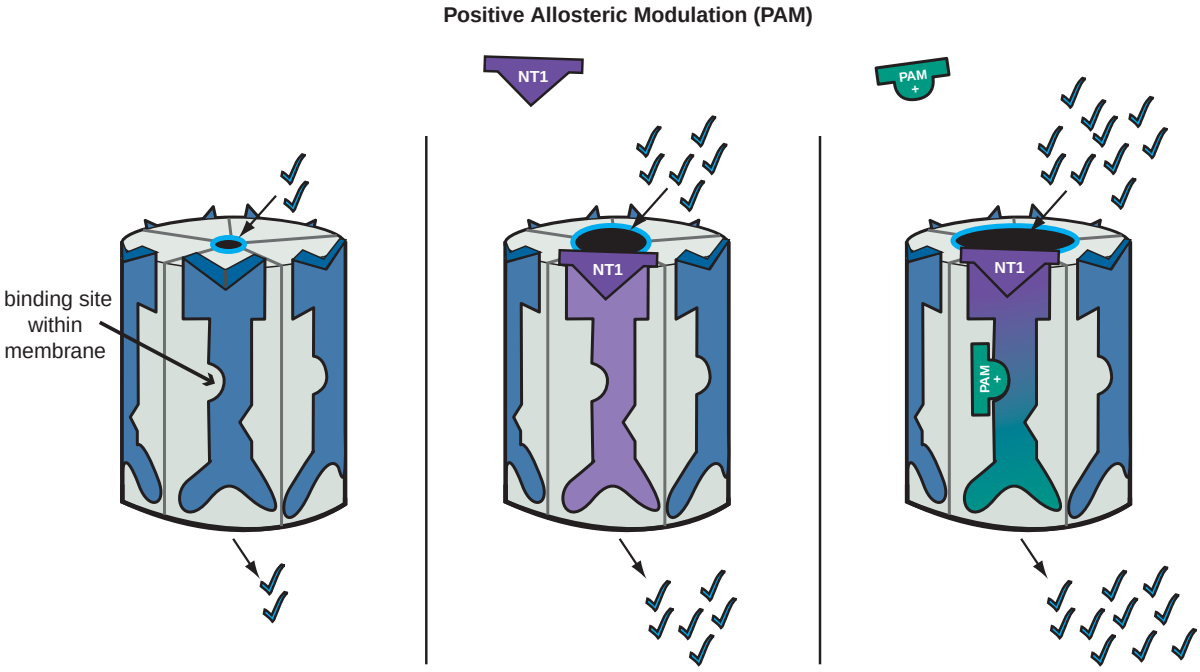


Figure 3-15. Opening, desensitizing, and inactivating by agonists. Agonists cause ligand-gated ion channels to open more frequently, increasing ion conductance in comparison to the resting state. Prolonged exposure to agonists can cause a ligand-gated ion channel to enter a desensitized state in which it no longer responds to the agonist even if it is still bound. Prompt removal of the agonist can reverse this state fairly quickly. However, if the agonist stays longer, it can cause a conformational change that leads to inactivation of the ion channel. This state is not immediately reversed when the agonist is removed.

enduringly that the receptors are not only rapidly desensitized, but enduringly inactivated, requiring hours in the absence of agonist to get back to the resting state. These transitions among various receptor states induced by agonists are shown in Figure 3-15. Desensitization of nicotinic receptors is discussed in further detail in Chapter 14.

Allosteric modulation: PAMs and NAMs

Ligand-gated ion channels are regulated by more than the neurotransmitter(s) that bind to them. That is, there are other molecules that are not neurotransmitters but that can bind to the receptor/ion-channel complex at different sites from where



When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a positive allosteric modulator (PAM) are bound to the receptor, the channel opens much more frequently, allowing more ions into the cell.

Figure 3-16. Positive allosteric modulators (PAMs). Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a PAM binds to its site while an agonist is also bound, the channel opens more frequently than when only the agonist is bound, therefore allowing more ions into the cell.

neurotransmitter(s) bind. These sites are called *allosteric* (literally, "other site") and ligands that bind there are called allosteric modulators. These ligands are modulators rather than neurotransmitters because they have little or no activity on their own in the absence of the neurotransmitter. Allosteric modulators thus only work in the presence of the neurotransmitter.

There are two forms of allosteric modulators – those that boost what the neurotransmitter does and are thus called positive allosteric modulators (PAMs), and those that block what the neurotransmitter does and are thus called negative allosteric modulators (NAMs).

Specifically, when PAMs or NAMs bind to their allosteric sites while the neurotransmitter is *not* binding to its site, the PAM and the NAM do nothing. However, when a PAM binds to its allosteric site while the neurotransmitter is sitting at its site, the PAM causes conformational changes in the ligand-gated ion channel that open the channel even further and more frequently than happens with a full agonist by itself (Figure 3-16). That is why the PAM is called "positive." Good examples of PAMs are benzodiazepines. These ligands boost the action of GABA at $GABA_A$ types of ligand-gated chloride ion channels. GABA binding to $GABA_A$ sites increases chloride ion flux by opening the ion channel, and benzodiazepines acting as agonists at benzodiazepine receptors elsewhere on the $GABA_A$ receptor complex cause the effect of GABA to be amplified in terms of chloride ion flux by opening the ion channel to a greater degree or more frequently. Clinically, this is exhibited as anxiolytic, hypnotic, anticonvulsant, amnestic, and muscle relaxant actions. In this example, benzodiazepines are acting as full agonists at the PAM site.

On the other hand, when a NAM binds to its allosteric site while the neurotransmitter resides at its agonist binding site, the NAM causes conformational

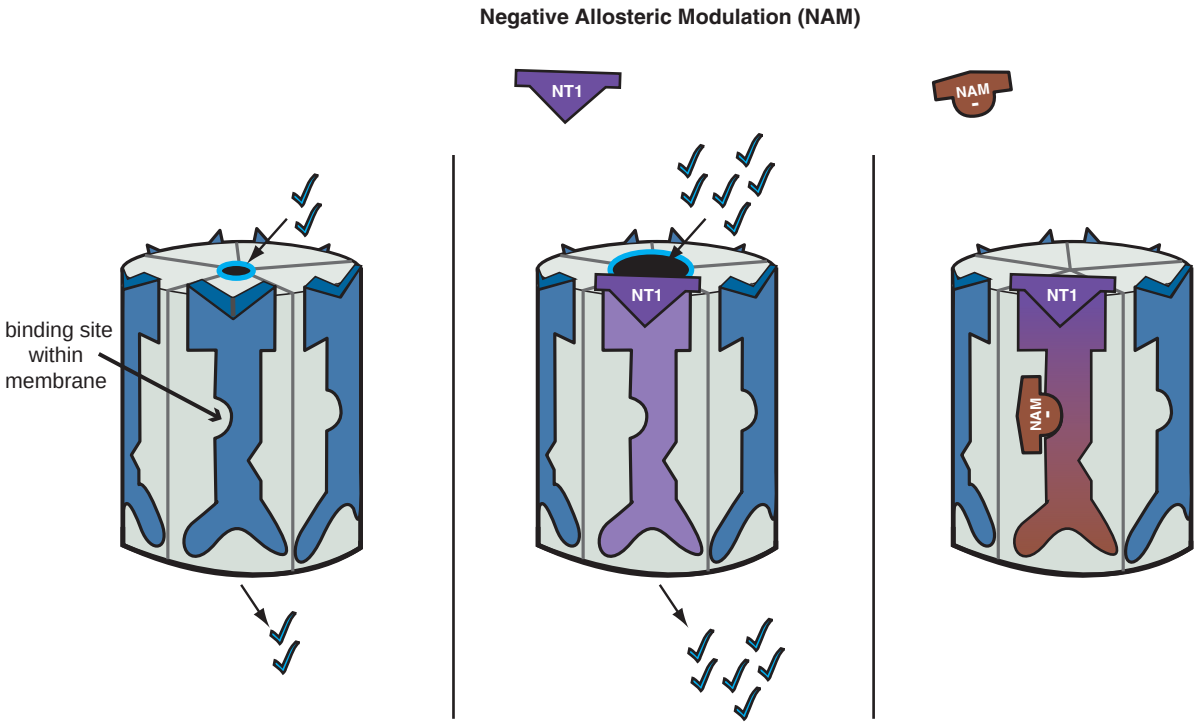


Figure 3-17. Negative allosteric modulators (NAMs). Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a NAM binds to its site while an agonist is also bound, the channel opens less frequently than when only the agonist is bound, therefore allowing fewer ions into the cell.

changes in the ligand-gated ion channel that block or reduce the actions that normally occur when the neurotransmitter acts alone (Figure 3-17). That is why the NAM is called "negative." One example of a NAM is a benzodiazepine inverse agonist. Although these are only experimental, as expected, they have the opposite actions of benzodiazepine full agonists and thus diminish chloride conductance through the ion channel so much that they cause panic attacks, seizures, and some improvement in memory – the opposite clinical effects of a benzodiazepine full agonist. Thus, the same allosteric site can have either NAM or PAM actions, depending upon whether the ligand is a full agonist or an inverse agonist. NAMs for NMDA receptors include phencyclidine (PCP, also called "angel dust") and its structurally related anesthetic agent ketamine. These agents bind to a site in the calcium channel, but can get into the channel to block it only when the channel is open. When either PCP or ketamine bind to their NAM site, they prevent glutamate/glycine cotransmission from opening the channel.

Voltage-sensitive ion channels as targets of psychopharmacological drug action

Structure and function

Not all ion channels are regulated by neurotransmitter ligands. Indeed, critical aspects of nerve conduction, action potentials, and neurotransmitter release are all mediated by another class of ion channels known as *voltage-sensitive* or *voltage-gated*; they are so called because their opening and closing are

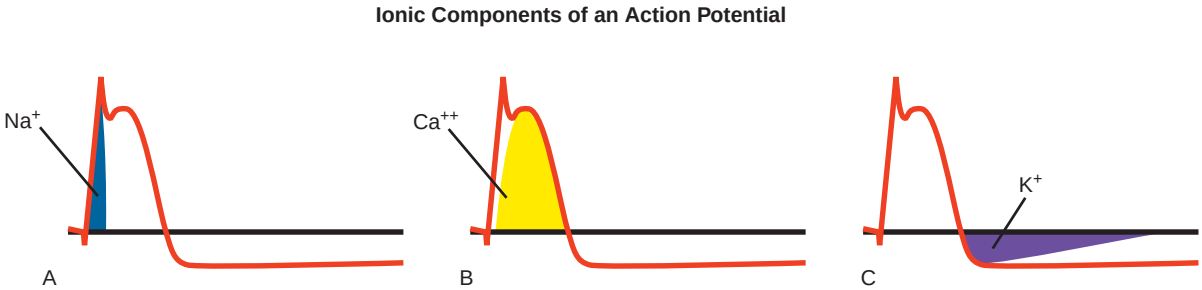


Figure 3-18. Ionic components of an action potential. The ionic components of an action potential are shown graphically here. First, voltage-sensitive sodium channels (VSSCs) open to allow an influx of "downhill" sodium into the negatively charged internal milieu of the neuron (A). The change of voltage potential caused by the influx of sodium triggers voltage-sensitive calcium channels (VSCCs) to open and allow calcium influx (B). Finally, after the action potential is gone, potassium enters the cell while sodium is pumped out, restoring the neuron's baseline internal electrical milieu (C).

regulated by the ionic charge or voltage potential across the membrane in which they reside. An electrical impulse in a neuron, also known as the action potential, is triggered by summation of the various neurochemical and electrical events of neurotransmission. These are discussed extensively in Chapter 1, which covers the chemical basis of neurotransmission and signal transduction.

The ionic components of an action potential are shown in Figure 3-18. The first phase is sodium rushing "downhill" into the sodium-deficient, negatively charged internal milieu of the neuron (Figure 3-18A). This is made possible when voltage-gated sodium channels open the gates and let the sodium in. A few milliseconds later, the calcium channels get the same idea, with their voltage-gated ion channels opened by the change in voltage potential caused by the sodium rushing in (Figure 3-18B). Finally, after the action potential is gone, during recovery of the neuron's baseline internal electrical milieu, potassium makes its way back into the cell through potassium channels while sodium is again pumped out (Figure 3-18C). It is now known or suspected that several psychotropic drugs work on voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs). These classes of ion channels will be discussed here. Potassium channels are less well known to be targeted by psychotropic drugs and will thus not be emphasized.

VSSCs (voltage-sensitive sodium channels)

Many dimensions of ion-channel structure are similar for VSSCs and VSCCs. Both have a "pore" that is the channel itself, allowing ions to travel from one side of the membrane to the other. However, voltage-gated ion channels have a more complicated structure than just a hole or pore in the membrane. These channels are long strings of amino acids, comprising subunits, and four different subunits are connected to form the critical pore, known as an α subunit. In addition, other proteins are associated with the four subunits, and these appear to have regulatory functions.

Let us now build a voltage-sensitive ion channel from scratch and describe the known functions for each part of the proteins that make up these channels. The subunit of a pore-forming protein has six transmembrane segments (Figure 3-19). Transmembrane segment 4 can detect the difference in charge across the membrane and is thus the most electrically sensitive part of the voltage-sensitive channel. Transmembrane segment 4 thus functions like a voltmeter, and when it detects a change in ion charge across the membrane, it can alert the rest of the protein and begin conformational changes of the ion channel to either open it or close it. This same general structure exists for both VSSCs (Figure 3-19A) and VSCCs (Figure 3-19B), but the exact amino acid sequences of the protein subunits are obviously different for VSSCs compared to VSCCs.

Each subunit of a voltage-sensitive ion channel has an extracellular amino acid loop between transmembrane segments 5 and 6 (Figure 3-19). This section of amino acids serves as an "ionic filter" and is located in a position so that it can cover the outside opening of the pore. This is illustrated as a colander configured molecularly to allow only sodium ions to filter through the sodium channel on the left and only calcium channels to filter through the calcium channel on the right (Figure 3-19).

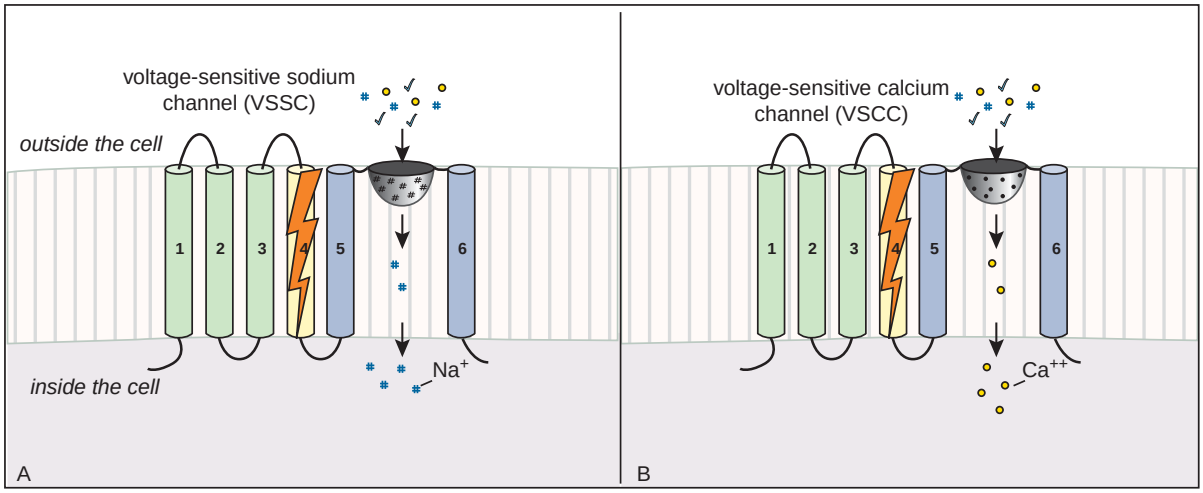


Figure 3-19. Ionic filter of voltage-sensitive sodium and calcium channels. The extracellular loop between transmembrane segments 5 and 6 of an α pore unit acts as an ionic filter (illustrated here as a colander). In the α pore unit of a voltage-sensitive sodium channel, the ionic filter allows only sodium ions to enter the cell (A). In the α pore unit of a voltage-sensitive calcium channel, the ionic filter allows only calcium ions to enter the cell (B).

Four copies of the sodium-channel version of this protein are strung together to form one complete ion-channel pore of a VSSC (Figure 3-20A). The cytoplasmic loops of amino acids that tie these four subunits together are sites that regulate various functions of the sodium channel. For example, on the connector loop between the third and fourth subunits of a VSSC, there are amino acids that act as a "plug" to close the channel. Like a ball on an amino acid chain, this "pore inactivator" stops up the channel on the inner membrane surface of the pore (Figure 3-20A and B). This is a physical blocking of the hole in the pore, and reminiscent of an old-fashioned bathtub plug stopping up the drain in a bathtub. The pore-forming unit of the VSSC is also shown as an icon in Figure 3-20B with a hole in the middle of the pore, and a pore inactivator ready to plug the hole from the inside.

Many figures in textbooks represent voltage-gated ion channels with the outside of the cell on the top of a figure; this is the way the ion channel is shown in Figure 3-20A and B. Here, we also show what the channel looks like when the inside of the cell is at the top of the figure, since throughout this book these channels will often be shown on presynaptic membranes where the inside of the neuron is up and the outside of the neuron, namely its synapse, is down, like the orientation represented in Figure 3-20C. In either case, the sodium is kept out of the neuron when the channel is closed or inactivated and the direction of sodium flow is into the neuron when the channel is open, activated, and the pore is not plugged up with the pore-inactivating amino acid loops.

Voltage-sensitive sodium channels may have one or more regulatory proteins, some of which are called β units, located in the transmembrane area and flanking the α pore-forming unit (Figure 3-20C). The function of these β subunits is not clearly established, but they may modify the actions of the α unit and thereby indirectly influence the opening and closing of the channel. It is possible that β units may be phosphoproteins and that their state of phosphorylation or dephosphorylation could regulate how much influence they exert on ion-channel regulation. Indeed, the α unit itself may also be a phosphoprotein, with the possibility that its own phosphorylation state could be regulated by signal transduction cascades and thus increase or decrease the sensitivity of the ion channel to changes in the ionic environment. This is discussed in Chapter 1 as part of the signal transduction cascade, and ion channels in some cases may act as third, fourth, or subsequent messengers triggered by neurotransmission. Both β subunits and the α subunit itself may have various sites where various psychotropic drugs act, especially anticonvulsants, some of which are also useful as mood stabilizers or as treatments for chronic pain. Specific drugs will be discussed in further detail in the chapters on mood stabilizers (Chapter 8) and pain (Chapter 10).

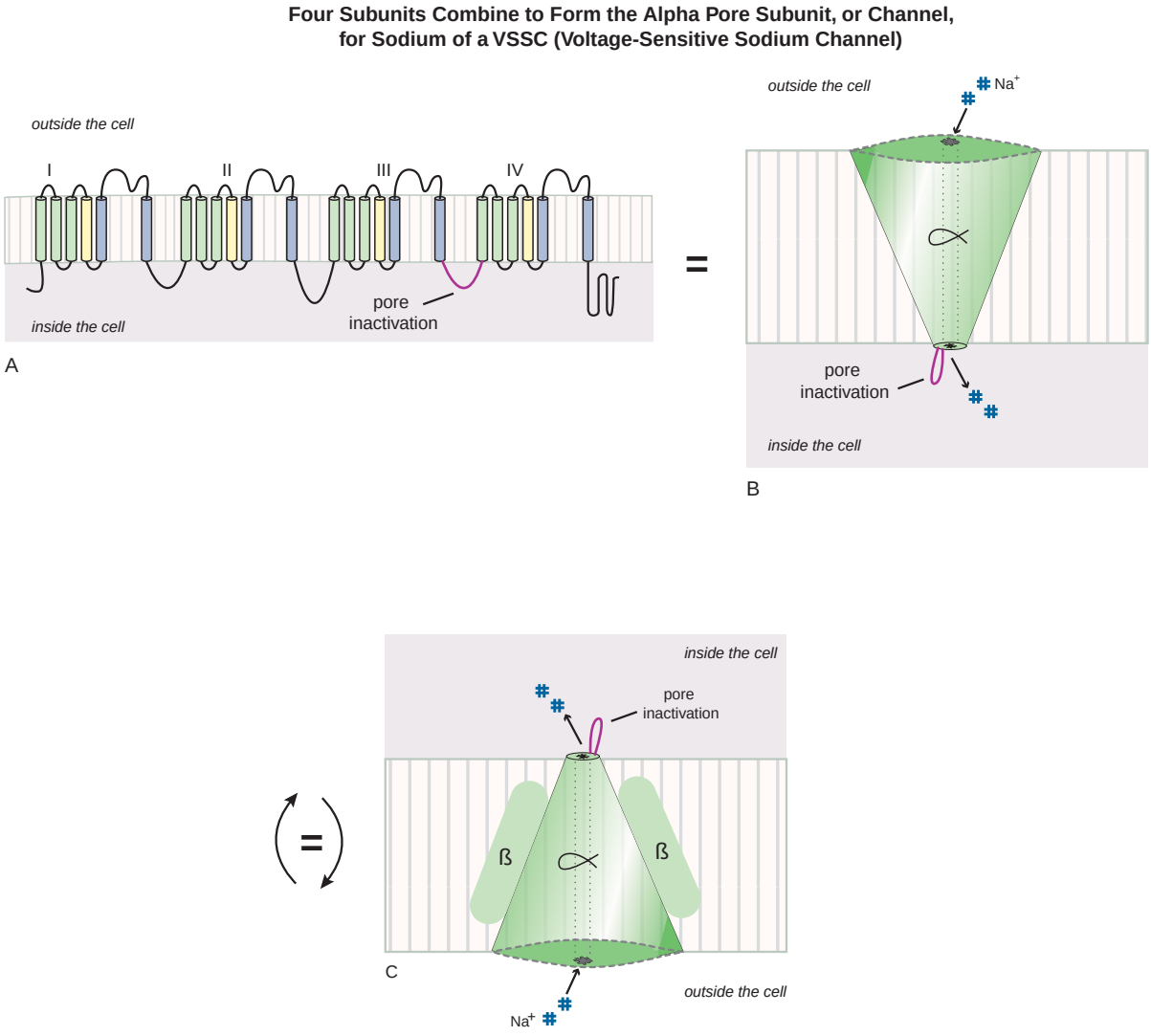


Figure 3-20. Alpha pore of voltage-sensitive sodium channel. The α pore of a voltage-sensitive sodium channel comprises four subunits (A). Amino acids in the intracellular loop between the third and fourth subunits act as a pore inactivator, "plugging" the channel. An iconic version of the α unit is shown here, with the extracellular portion on top (B) and with the intracellular portion on top (C).

Three different states of a VSSC are shown in Figure 3-21. The channel can be open and active, a state allowing maximum ion flow through the α unit (Figure 3-21A). When a sodium channel needs to stop ion flow, it has two states that can do this. One state acts very quickly to flip the pore inactivator into place, stopping ion flow so fast that the channel has not yet even closed (Figure 3-21B). Another state of inactivation actually closes the channel with conformational changes in the ion channel's shape (Figure 3-21C). The pore inactivation mechanism may be for fast inactivation, and the channel closing mechanism may be for a more stable state of inactivation, but it is not entirely clear.

There are many subtypes of sodium channels, but the details of how they are differentiated from each other by location in the brain, functions, and drug actions are only beginning to be clarified. For the psychopharmacologist, what is now of interest is the fact that various sodium channels may be the sites of action of several anticonvulsants, some of which have mood-stabilizing and pain-reducing properties. Most currently available anticonvulsants probably have multiple sites of action, including multiple sites of

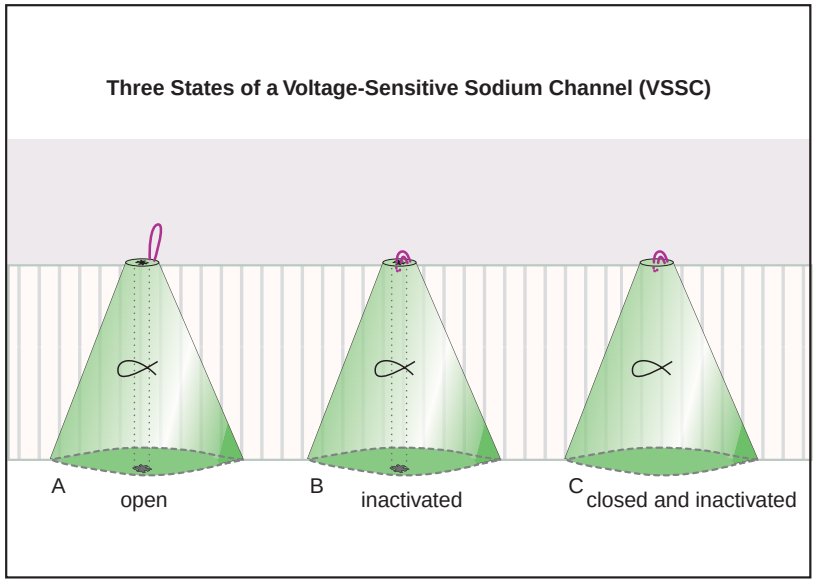


Figure 3-21. States of a voltage-sensitive sodium channel. VSSCs can be in the open state, in which the ion channel is open and active and ions flow through the α unit (left). They may also be in an inactivated state, in which the channel is not yet closed but has been "plugged" by the pore inactivator, preventing ion flow (middle). Finally, conformational changes in the ion channel can cause it to close, the third state (right).

action at multiple types of ion channels. The specific actions of specific drugs will be discussed in the chapters that cover specific disorders.

VSCCs (voltage-sensitive calcium channels)

Many aspects of VSCCs and VSSCs are similar – not just their names. Like their sodium-channel cousins, the voltage-sensitive calcium channels also have subunits with six transmembrane segments, with segment 4 a voltmeter and with the extracellular amino acids connecting segments 5 and 6 acting as an ionic filter – only this time as a colander allowing calcium to come into the cell, not sodium (Figure 3-19B). Obviously, the exact sequence of amino acids differs between a sodium channel and a calcium channel, but they have a very similar overall organization and structure.

Just like voltage-gated sodium channels, VSCCs also string together four of their subunits to form a pore, in this case called an α_1 unit (Figure 3-22). The connecting string of amino acids also has functional activities that can regulate calcium-channel functioning, but in this case the functions are different from those for sodium channels. That is, there is no pore inactivator working as a plug for the VSCC, as was described above for the VSSC; instead, the amino acids connecting the second and third subunits of the voltage-sensitive calcium channel work as a "snare" to hook up with synaptic vesicles and regulate the release of neurotransmitter into the synapse during synaptic neurotransmission (Figures 3-22A and 3-23). The orientation of the calcium channel in Figure 3-22B is with the outside of the cell at the top of the page, and this is switched in Figure 3-22C so that the inside of the cell is now at the top of the page, so the reader can see how these channels might look in various configurations in space. In all cases, the direction of ion flow is from outside the cell to the inside when that channel opens to allow ion flow to occur.

Several proteins flank the α_1 pore-forming unit of a VSCC, called γ, β, and $\alpha_2\delta$. Shown in Figure 3-22C are γ units that span the membrane, cytoplasmic β units, and a curious protein called $\alpha_2\delta$, because it has two parts: a δ part that is transmembrane, and an α_2 part that is extracellular (Figure 3-22C). The functions of all these proteins associated with the α_1 pore-forming unit of a voltage-sensitive calcium channel are just beginning to be understood, but already it is known that the $\alpha_2\delta$ protein is the target of certain psychotropic drugs, such as the anticonvulsants pregabalin and gabapentin, and that this $\alpha_2\delta$ protein may be involved in regulating conformational changes of the ion channel to change the way the ion channel opens and closes.

As would be expected, there are several subtypes of VSCCs (Table 3-4). The vast array of voltage-sensitive calcium channels indicates that the term "calcium channel" is much too general, and in fact

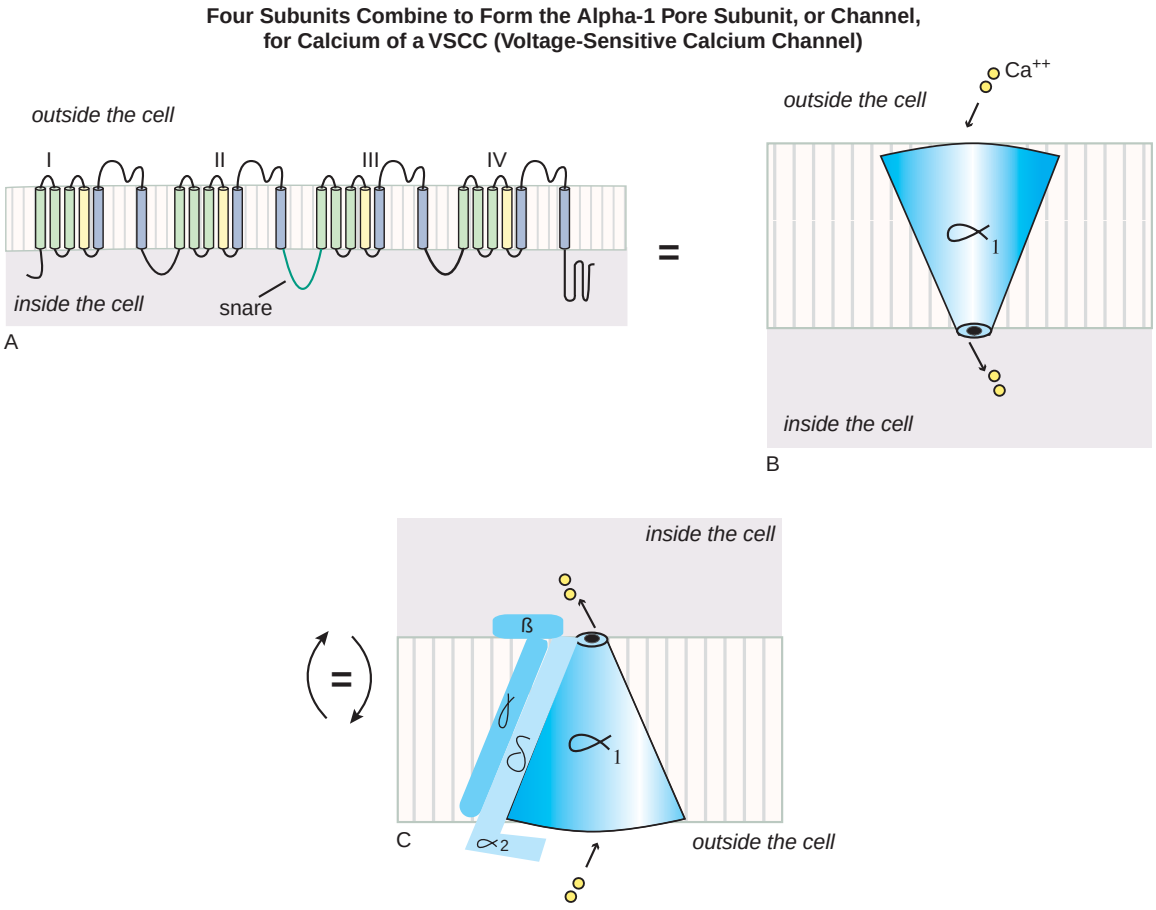


Figure 3-22. Alpha-1 pore of voltage-sensitive calcium channel. The α pore of a voltage-sensitive calcium channel, termed an α_1 unit, comprises four subunits (A). Amino acids in the cytoplasmic loop between the second and third subunits act as a snare to connect with synaptic vesicles, thereby controlling neurotransmitter release (A). An iconic version of the α_1 unit is also shown here, with the extracellular portion on top (B) and with the intracellular portion on top (C).

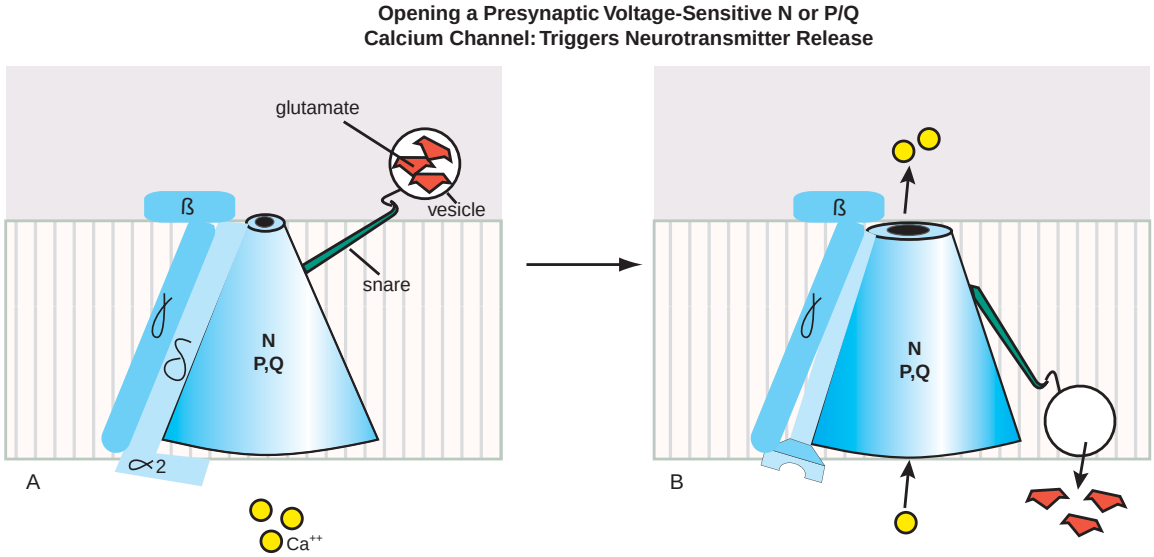


Figure 3-23. N and P/Q voltage-sensitive calcium channels. The voltage-sensitive calcium channels that are most relevant to psychopharmacology are termed N and P/Q channels. These ion channels are presynaptic and involved in the regulation of neurotransmitter release. The intracellular amino acids linking the second and third subunits of the α_1 unit form a snare that hooks onto synaptic vesicles (A). When a nerve impulse arrives, the snare "fires," leading to neurotransmitter release (B).

Table 3-4 Subtypes of voltage-sensitive calcium channels (VSCCs)

Type	Pore-forming subunit	Location	Function
L	Ca_v 1.2, 1.3	Cell bodies, dendrites	Gene expression, synaptic integration
N	Ca_v 2.2	*Nerve terminals* Dendrites, cell bodies	*Transmitter release* Synaptic integration
P/Q	Ca_v 2.1	*Nerve terminals* Dendrites, cell bodies	*Transmitter release* Synaptic integration
R	Ca_v 2.3	*Nerve terminals* Cell bodies, dendrites	*Transmitter release* Repetitive firing, synaptic integration
T	Ca_v 3.1, 3.2, 3.3	Cell bodies, dendrites	Pacemaking, repetitive firing, synaptic integration

can be confusing. For example, calcium channels associated with the ligand-gated ion channels discussed in the previous section, especially those associated with glutamate and nicotinic cholinergic ionotropic receptors, are members of an entirely different class of ion channels from the voltage-sensitive calcium channels under discussion here. As we have mentioned, calcium channels associated with this previously discussed class of ion channels are called ligand-gated ion channels, ionotropic receptors, or ion-channel-linked receptors, to distinguish them from VSCCs.

The specific subtypes of VSCCs of most interest to psychopharmacology are those that are presynaptic, that regulate neurotransmitter release, and that are targeted by certain psychotropic drugs. This subtype designation of VSCCs is shown in Table 3-4, and such channels are known as N or P/Q channels.

Another well-known subtype of VSCC is the L channel. This channel exists not only in the central nervous system, where its functions are still being clarified, but also on vascular smooth muscle, where it regulates blood pressure and where a group of drugs known as dihydropyridine "calcium channel blockers" interact as therapeutic antihypertensives to lower blood pressure. R and T channels are also of interest, and some anticonvulsants and psychotropic drugs may also interact there, but the exact roles of these channels are still being clarified.

Presynaptic N and P/Q VSCCs have a specialized role in regulating neurotransmitter release because they are linked by molecular "snares" to synaptic vesicles (Figure 3-23). That is, these channels are literally hooked to synaptic vesicles. Some experts think of this as a cocked gun – loaded with neurotransmitters packed in a synaptic vesicle bullet (Figure 3-23A) ready to be fired at the postsynaptic neuron as soon as a nerve impulse arrives (Figure 3-23B). Some of the structural details of the molecular links – namely, with snare proteins – that connect the N and P/Q VSCCs with the synaptic vesicle are shown in Figure 3-24. If a drug interferes with the ability of the channel to open and let in calcium, the synaptic vesicle stays tethered to the voltage-gated calcium channel. Neurotransmission can thus be prevented, which may be desirable in states of excessive neurotransmission, such as pain, seizures, mania, or anxiety. This may explain the action of certain anticonvulsants.

Indeed, it is neurotransmitter release that is the *raison d'être* for presynaptic voltage-sensitive N and P/Q channels. When a nerve impulse invades the presynaptic area, this causes the charge across the membrane to change, in turn opening the VSCC, allowing calcium to enter; this makes the synaptic vesicle dock into and merge with the presynaptic membrane, spewing its neurotransmitter contents into the synapse to effect neurotransmission (Figures 3-25 and 3-26). This conversion of an electrical impulse into a chemical message is triggered by calcium and sometimes called excitation–secretion coupling.

Anticonvulsants are thought to act at various VSSCs and VSCCs and will be discussed in further detail in the relevant clinical chapters. Many of these anticonvulsants have several uses in psychopharmacology, from chronic pain to migraine, from bipolar mania to bipolar depression to bipolar maintenance, and possibly as anxiolytics and sleep aids. These specific applications and more details about hypothetical mechanisms of action are explored in depth in the clinical chapters dealing with the various psychiatric disorders.

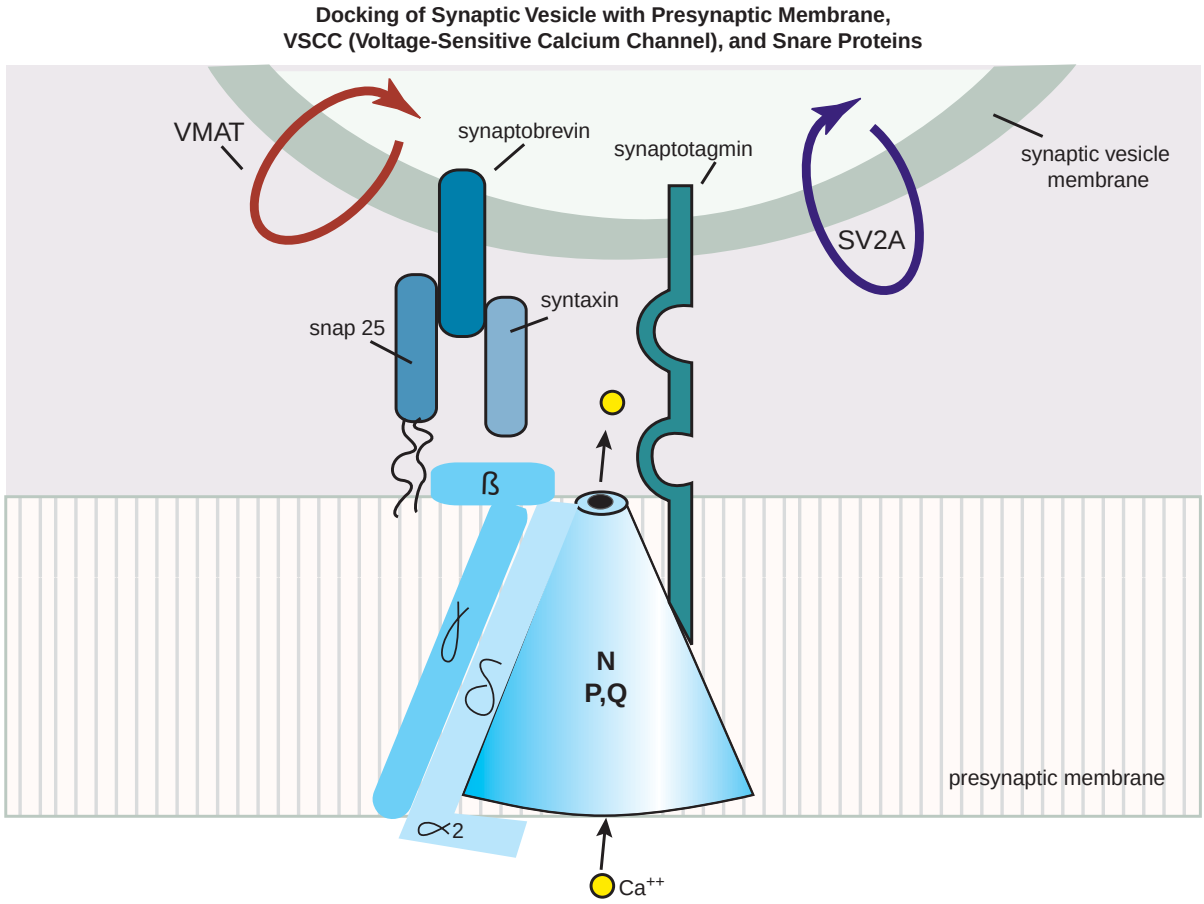


Figure 3-24. Snare proteins. Proteins that link the voltage-sensitive calcium channel to the synaptic vesicle, called snare proteins, are shown here; they include SNAP 25, synaptobrevin, syntaxin, and synaptotagmin. A VMAT (vesicular monoamine transporter) is shown on the left. Another transporter, SV2A, is shown on the right. The mechanism of this transporter is not yet clear, but the anticonvulsant levetiracetam is known to bind to this site.

Ion channels and neurotransmission

Although the various subtypes of ligand-gated and voltage-gated ion channels are presented separately, the reality is that they work cooperatively during neurotransmission. When the actions of all these ion channels are well orchestrated, brain communication becomes a magical mix of electrical and chemical messages made possible by ion channels. The coordinated acts of ion channels during neurotransmission are illustrated in Figures 3-25 and 3-26.

The initiation of chemical neurotransmission by a neuron's ability to integrate all of its inputs and then translate them into an electrical impulse is presented in Chapter 1. We now show how ion channels are involved in this process. After a neuron receives and integrates its inputs from other neurons, it then encodes them into an action potential, and that nerve impulse is next sent along the axon via voltage-sensitive sodium channels that line the axon (Figure 3-25).

The action potential could be described as lighting a fuse, with the fuse burning from the initial segment of the axon to the axon terminal. Movement of the burning edge of the fuse is carried out by a sequence of VSSCs that open one after the other, allowing sodium to pass into the neuron and then carrying the electrical impulse along to the next VSSC in line (Figure 3-25). When the electrical impulse reaches the axon terminal, it meets voltage-sensitive calcium channels in the presynaptic neuronal membrane, already loaded with synaptic vesicles and ready to fire (see axon terminal of neuron A in Figure 3-25).

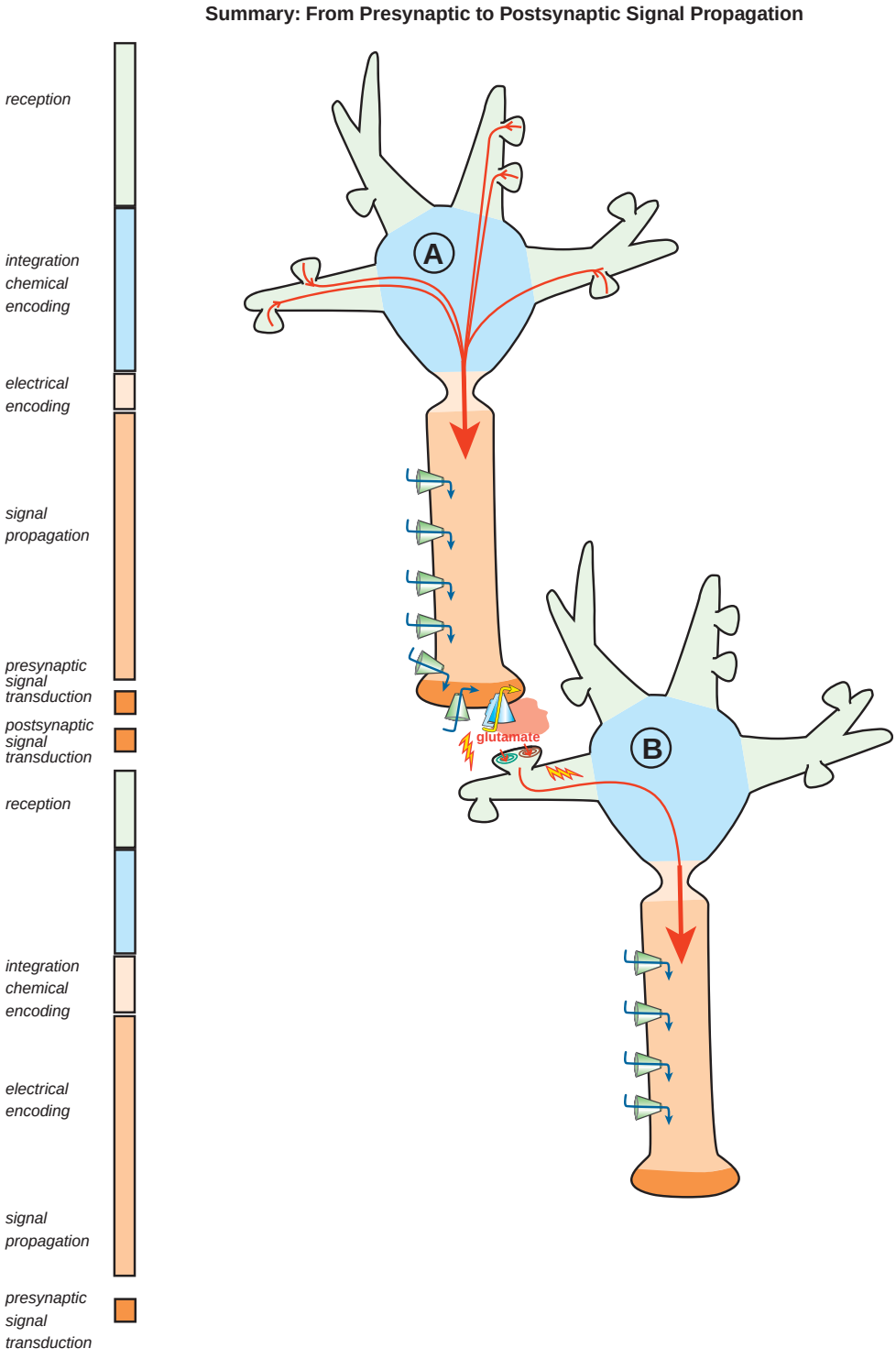


Figure 3-25. Signal propagation. Summary of signal propagation from presynaptic to postsynaptic neuron. A nerve impulse is generated in neuron A, and the action potential is sent along the axon via voltage-sensitive sodium channels until it reaches voltage-sensitive calcium channels linked to synaptic vesicles full of neurotransmitters in the axon terminal. Opening of the voltage-sensitive calcium channel and consequent calcium influx causes neurotransmitter release into the synapse. Arrival of neurotransmitter at postsynaptic receptors on the dendrite of neuron B triggers depolarization of the membrane in that neuron and, consequently, postsynaptic signal propagation.

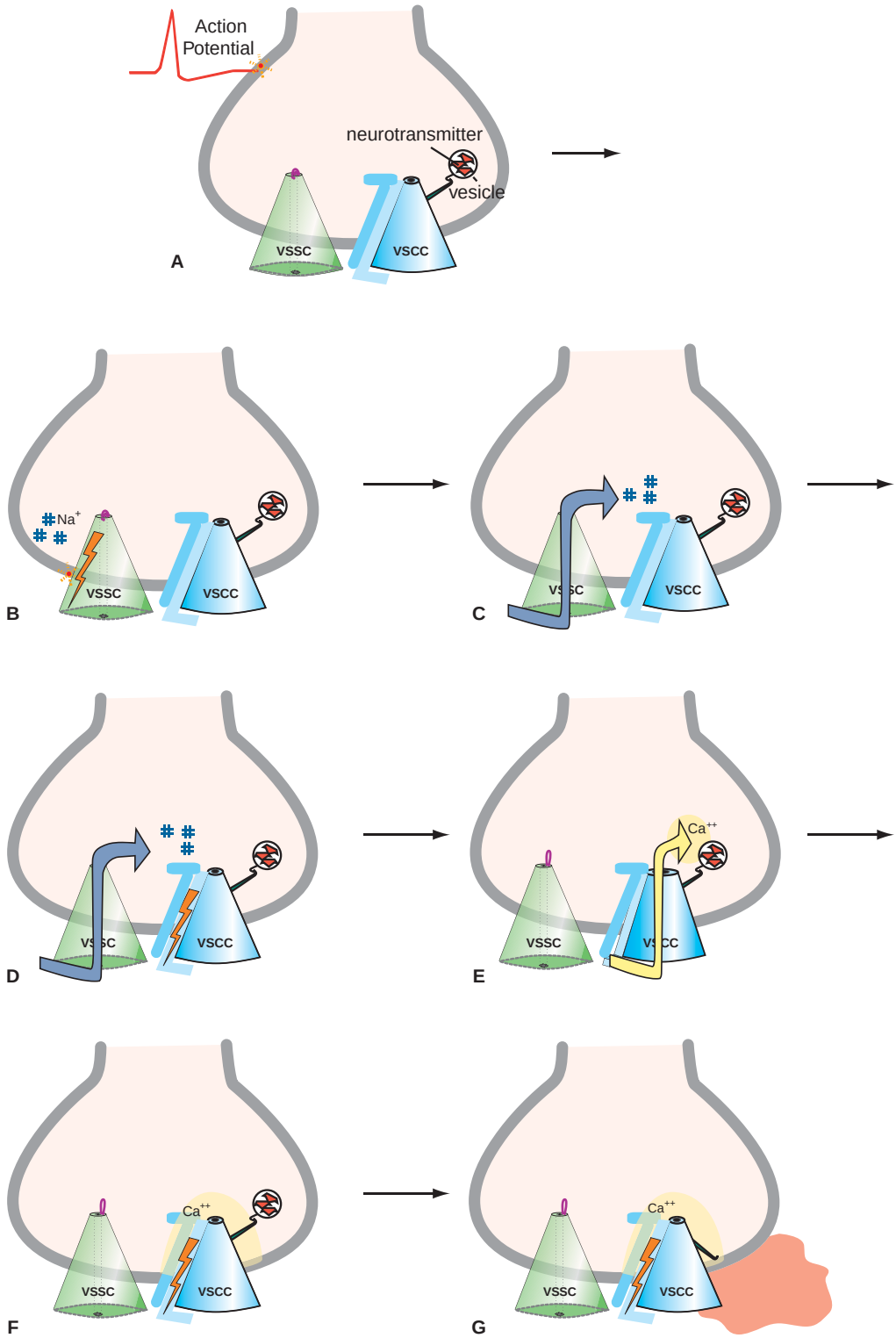


Figure 3-26. Excitation–secretion coupling. Details of excitation–secretion coupling are shown here. An action potential is encoded by the neuron and sent to the axon terminal via voltage-sensitive sodium channels along the axon (A). The sodium released by those channels triggers a voltage-sensitive sodium channel at the axon terminal to open (B), allowing sodium influx into the presynaptic neuron (C). Sodium influx changes the electrical charge of the voltage-sensitive calcium channel (D), causing it to open and allow calcium influx (E). As the intraneuronal concentration of calcium increases (F), the synaptic vesicle is caused to dock and merge with the presynaptic membrane, leading to neurotransmitter release (G).

When the electrical impulse is detected by the voltmeter in the voltage-sensitive calcium channel, it opens the calcium channel, allowing calcium to enter, and bang! – the neurotransmitter is released in a cloud of synaptic chemicals from the presynaptic axon terminal via excitation–secretion coupling (see axon terminal of neuron A in Figure 3-25 and enlarged illustrations of this in Figure 3-26). Details of this process of excitation–secretion coupling are shown in Figure 3-26, beginning with the action potential about to invade the presynaptic terminal and with a closed VSSC sitting next to a closed but poised VSCC snared to its synaptic vesicle (Figure 3-26A). As the nerve impulse arrives in the axon terminal, it first hits the VSSC as a wave of positive sodium charges delivered by the openings of upstream sodium channels, which are detected by the sodium channel's voltmeter (Figure 3-26B). This opens the last sodium channel shown, allowing sodium to enter (Figure 3-26C). The consequence of this sodium entry is to change the electrical charge near the calcium channel; this is then detected by the VSCC's voltmeter (Figure 3-26D). Next, the calcium channel opens (Figure 3-26E). At this point, chemical neurotransmission has now been irreversibly triggered, and the translation of an electrical message into a chemical message has begun. Calcium entry from the VSCC now increases the local concentrations of this ion in the vicinity of the VSCC, the synaptic vesicle, and the neurotransmitter release machinery (Figure 3-26F). This causes the synaptic vesicle to dock into the inside of the presynaptic membrane, then merge with it, spewing its neurotransmitter contents out of the membrane and into the synapse (Figure 3-26G). This amazing process occurs almost instantaneously and simultaneously from many VSCCs releasing neurotransmitter from many synaptic vesicles.

By now, only about half of the sequential phenomena of chemical neurotransmission have been described. The other half occur on the other side of the synapse. That is, reception of the released neurotransmitter now occurs in neuron B (Figure 3-25), which can set up another nerve impulse in neuron B. This whole process – from the generation of a nerve impulse and its propagation along neuron A to its nerve terminal, then sending chemical neurotransmission to neuron B, and finally propagating this second nerve impulse along neuron B – is summarized in Figure 3-25. Voltage-sensitive sodium channels in presynaptic neuron A propagate the impulse there, and then voltage-sensitive calcium channels in presynaptic neuron A release the neurotransmitter glutamate. Ligand-gated ion channels on dendrites in postsynaptic neuron B next receive this chemical input, and translate this chemical message back into a nerve impulse propagated in neuron B by voltage-sensitive sodium channels in that neuron. Also, ligand-gated ion channels in postsynaptic neuron B translate the glutamate chemical signal into another type of electrical phenomenon called long-term potentiation, to cause changes in the function of neuron B.

Summary

Ion channels are key targets of many psychotropic drugs. This is not surprising, because these targets are key regulators of chemical neurotransmission and the signal transduction cascade.

There are two major classes of ion channels: ligand-gated ion channels and voltage-sensitive ion channels. The opening of ligand-gated ion channels is regulated by neurotransmitters, whereas the opening of voltage-sensitive ion channels is regulated by the charge across the membrane in which they reside.

Ligand-gated ion channels are both ion channels and receptors. They are also commonly called ionotropic receptors as well as ion-channel-linked receptors. One subclass of ligand-gated ion channels has a pentameric structure and includes $GABA_A$, nicotinic cholinergic, serotonin 3, and glycine receptors. The other subclass of ligand-gated ion channels has a tetrameric structure, and includes many glutamate receptors, including the AMPA, kainate, and NMDA subtypes.

Ligands act at ligand-gated ion channels across an agonist spectrum, from full agonist, to partial agonist, to antagonist, to inverse agonist. Ligand-gated ion channels can be regulated not only by neurotransmitters acting as agonists, but also by molecules interacting at other sites on the receptor, either boosting the action of neurotransmitter agonists as positive allosteric modulators (PAMs), or diminishing the action of neurotransmitter agonists as negative allosteric modulators (NAMs). In addition, these receptors exist in several states, from open, to resting, to closed, to inactivated, to desensitized.

The second major class of ion channels is called either voltage-sensitive or voltage-gated, since they are opened and closed by the voltage charge across the membrane. The major channels from this class that are of interest to psychopharmacologists are the voltage-sensitive sodium channels (VSSCs) and the voltage-sensitive calcium channels (VSCCs). Numerous anticonvulsants bind to various sites on these channels and may exert their anticonvulsant actions by this mechanism, as well as their actions as mood stabilizers, treatments for chronic pain, anxiolytics, and sleep medications.